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Grau de Química

Treball Final de Grau

A study on the thermal stability of carbamate and carbonate derivatives of *N*-(pyridin-2-yl)-2-aminoethanol
Estudi de l'estabilitat tèrmica de derivats carbamats i carbonats de *N*-(piridin-2-il)-2-amionetanol

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Juny 2021

Universitat de Barcelona

B:KC Barcelona Knowledge Campus
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Si goséssiu saber tant com goseu posseir!

Carles Riba i Bracons

En primer lloc vull donar les gràcies al Dr. Ernesto Nicolàs i al Marcos Alvarez per l'esforç i la disposició d'ajudar-me i guiar-me sempre que ho he necessitat.

A la meva mare, pare, germà i família per recolzar-me i animar-me en els moments més durs i bons que he viscut al llarg d'aquests anys, sense el vostre suport res seria possible.

I per últim, a les meves companyes , sense vosaltres aquesta etapa no hagués sigut el mateix, per seguir-nos recolzant allà on ens portin els nostres camins.

REPORT

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1. SUMMARY

Currently, research on controlled selective release of drugs for the treatment of diseases such as cancer is a point of interest. In this sense, thermolabile ligands are a nice choice for binding the drug to a carrier in order to release it when desired by using a suitable source of heat. The Nanoscience and Bioinorganic Chemistry group (nanoBIC) of the Department of Inorganic and Organic Chemistry is investigating a system made of magnetic nanoparticles containing a 2-aminopyridine derivative as a thermolabile ligand for controlled drug release by means of an external magnetic field.

The present Degree Final Work has been carried out in the framework of a collaboration between the Synthetic Methodology Applied to Bioactive Compounds group (SMBioCom) of the same department and the research group above mentioned. In this project, the 2-aminopyridine derivative of methyl 4-[*N*-(2-hydroxyethyl)-*N*-(pyridin-2-yl)aminomethyl] benzoate has been studied as precursor of potentially thermolabile carbamates or carbonates. Thus, this derivative has been synthesized and used to prepare some carbamate/carbonate derivatives. The thermal decomposition of these derivatives by intramolecular cyclization with the concomitant release of the corresponding alcohol(carbonate) or amine (carbamate) has been studied by ^{1}H-NMR.

Keywords: thermolabile carbonates, thermolabile carbamates, carbonyldiimidazole, MW assisted nucleophiilc substitutions

2. RESUM

Actualment, la investigació sobre l'alliberament selectiu controlat de fàrmacs per al tractament de malalties com el càncer és un tema d'interès. En aquest àmbit, els lligands termolàbils són una bona opció per unir el fàrmac a un portador per alliberar-lo quan es desitgi mitjançant una font de calor adequada. El grup de Nanociència i Química Bioinorgànica (nanoBIC) del Departament de Química Inorgànica i Orgànica investiga un sistema format per nanopartícules magnètiques que contenen un derivat de 2-aminopiridina com a lligand termolàbil per a l'alliberament controlat de fàrmacs mitjançant un camp magnètic extern.

El present Treball Final de Grau s'ha dut a terme amb el marc d'una col·laboració entre el grup de Metodologia Sintètica Aplicada a Productes Bioactius (SMBioCom) del mateix departament i el grup de recerca anteriorment esmentat. En aquest projecte, s'ha estudiat el derivat de 2-aminopiridina del metil 4-[*N*-(2-hidroxietil)-*N*-(piridin-2-il)aminometil] benzoat com a precursor de carbamats o carbonats potencialment termolàbils. Així doncs, aquest derivat s'ha sintetitzat i utilitzat per preparar alguns derivats de carbamat/carbonat. La descomposició tèrmica d'aquests derivats per ciclació intramolecular amb l'alliberament del corresponent alcohol (carbonat) o amina (carbamat) ha estat estudiada per ^{1}H-RMN.

Paraules clau: carbonats termolàbils, carbamats termolàbils, carbodiimidazol, substitucions nucleofíliques assistides per MW

3. INTRODUCTION

Nowadays, the conventional administration drugs for disease treatments are either oral intake or injection. These methods have many disadvantages, specially related to limited effectiveness and lack of selectivity. Therefore, modern methods therapy absorptions are currently a point of interest. The controlled drug delivery system (DDS) is a formulation or a device that enables the introduction and transportation of a therapeutic substance inside an organism which, by controlling the rate, time and place of release, improves greatly its efficacy and safety. A possible controlled DDS are nanocarriers, which can be used as delivery tools for a bioactive compound.[1] The chance of improving the efficacy of the drug, lower the toxicity and control its biodistribution makes them an accurate choice.[2]

A controlled drugs release from nanocarriers can be achieved by different physiological changes such as pH, osmolality, via enzymatic activity and temperature,[1] being the last one of the most promising approaches.

In the last decade, the studies of thermolabile protecting groups (TPG) have been a point of interest due to the application of hydroxyl, amine and phosphate functional groups in organic synthesis.

The first thermal deprotection was made for phosphate groups during the synthesis of nucleic acids.[3][4] One of the first remarkable TPG designed was 4-oxopentyl because its properties of thermal stability and economical protection of phosphate and thiophosphate centres for the solid-phase oligodeoxyribonucleotide synthesis (**Figure 1**). The removal of this group involves an intramolecular cyclodeesterification induced by heating or ammonia gas in this case. Although it was dismissed due to the high thermal stability of its derivates (90 ºC). [5]

In the latest 2000-decade, Chmielewski et al. investigated 2-aminopyridyl system, (**Figure 2**) for thermolabile protection.[3] This new class of thermolabile groups have proved to be efficient as hydroxyl protecting groups for the phosphate group of nucleotides.

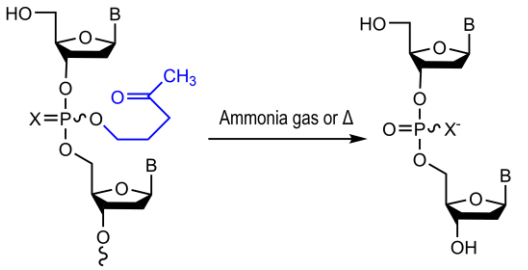
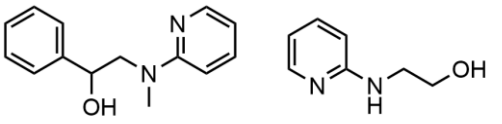


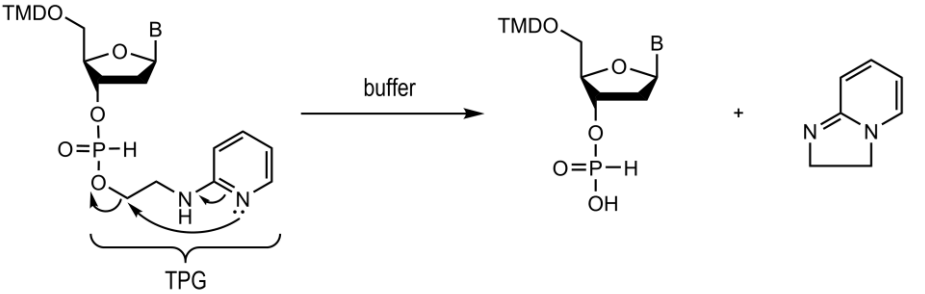
Figure 1. Deprotection of proposed 4-oxopentyl protecting group in solid-phase oligodeoxyribonucleotide synthesis. X=O or S.



A B

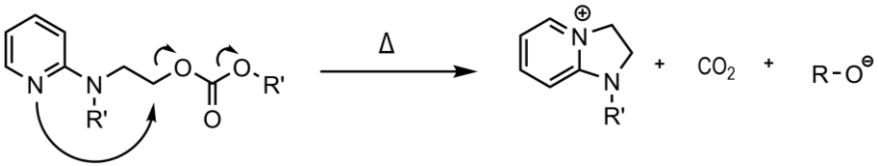
Figure 2. The 2-aminopyridyl system used for the thermolabile protection: 2-[*N*-Methyl-*N*-(2-pyridyl)]amino-1-phenylethanol (**A**) and *N*-(pyridyl-2-yl)aminoethanol (**B**).

This investigation revealed a new two-step mechanism named 'click-clack', where the term 'click' is related to an efficient nucleophilic substitution favoured by the presence of a good leaving group, and the term 'clack' is related to the simultaneous formation of a 5-membered ring under mild acidic conditions (**Scheme 1**). [6]



Scheme 1. Mechanism of the deprotection through the "Click-Clack" reaction approach. B is related to the nucleobase Thy.

Then, some findings showed that **A** could be a good candidate for thermolytic deprotection when hydroxyl groups were protected as carbonates. Carbonate decomposition was accomplished at 90 ºC in an hour by means of an intramolecular cyclization driven by the formation of a five-membered ring to give a cationic heterocycle with simultaneous release of CO_2 and the alkoxide (**Scheme 2**).[3]

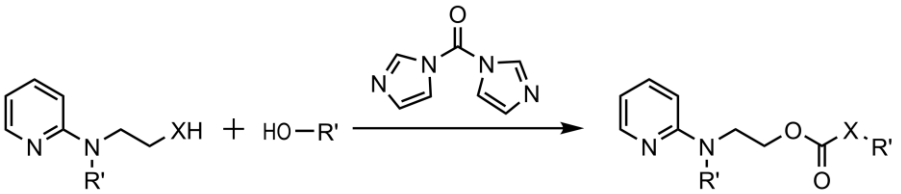


Scheme 2. Mechanism of thermal deprotection of an alcohol.

These results moved to the nanoBIC group of the Department of Inorganic and Organic Chemistry of the University of Barcelona, led by Dr. Patrick Gámez, to start a project to design carbonate and carbamate thermolabile linkers based on the 2-aminopyridyl moiety for controlled drug release. In this project, the external stimulus for drug release would be the thermal deprotection due the magnetic properties of nanoparticles (NP) made of magnetite (Fe_3O_4). Heat can be produced by applying radiofrequency irradiation with an external magnetic field to the NP. [7] That is, the drug is pretended to be covalently attached to the linker and the NP, so that the heat generated by the application of an external field could release the drug.

The synthetic methodology designed by the nanoBIC project for carbamates and carbonates is carried out using 1,1'-carbonyldiimidazole (CDI). CDI is an activating agent often used for acylation, particularly for the formation of amide bounds, which is safe and a commercially available.[8] This reagent is greatly sensitive to degradation by atmospheric moisture turning into imidazole and carbon dioxide because of its high reactivity, but it is considered one of the most eco-friendly activating agents.

CDI is a good alternative for the synthesis of small molecules because of its advantages as its ease of handling (as it is a solid) and its relatively low toxicity compared to the commonly used toxic isocyanates, triphosgene, or chloroformates.[9] Therefore, for the carbonate or carbamate synthesis of a TPG based on 2-aminopyridyl is a promising agent.[9]



Scheme 3. Synthesis of carbonates and carbamates using CDI.

Concerning to the 2-aminopyridyl derivative, the strategy purposed by the nanoBIC group is to use methyl 4-[*N*-(2-hydroxyethyl)-*N*-(pyridin-2-yl)aminomethyl] benzoate (**2**) because its hydrolysis produces a carboxylic group through which the linker can be anchored to the magnetic nanoparticle (MNP) (**Figure 3**).

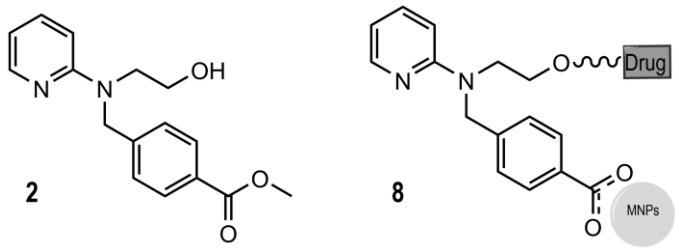


Figure 3. Structure of the 2-aminopyridyl derivative (**2**) and nanosystem designed by nanoBIC's group (**8**).

4. OBJECTIVES

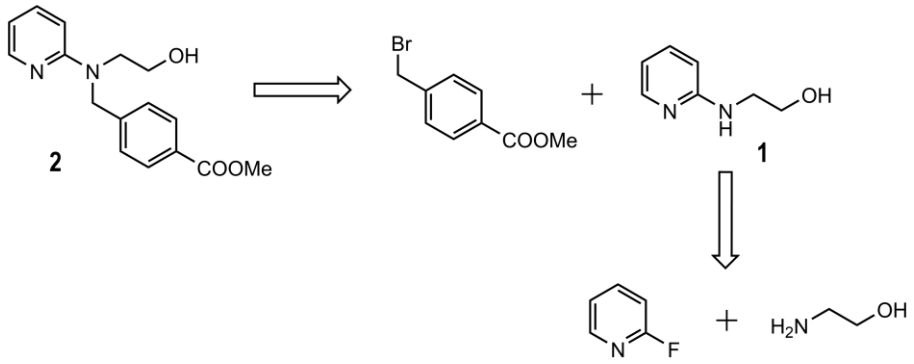
This Final Degree Work follows the previous studies of Aida López about the optimization of the precursor's synthesis and the thermal behaviour of different carbonate and carbamate derivatives of methyl 4-[*N*-(2-hydroxyethyl)-*N*-(pyridin-2-yl)aminomethyl] benzoate.

The objective of this Final Degree Work has been to progress in the research's project of the nanoBIC group, synthesising the thermolabile ligand methyl 4-[*N*-(2-hydroxyethyl)-*N*-(pyridin-2-yl)aminomethyl]benzoate and some carbamate/carbonate derivatives to perform the study of thermal behaviour of these molecules.

5. RESULTS AND DISCUSSION

5.1. SYNTHESIS OF METHYL 4-[*N*-(2-HYDROXYETHYL)-*N*-(PYRIDYL-2-YL)AMINOETHYL]BENZOATE (2)

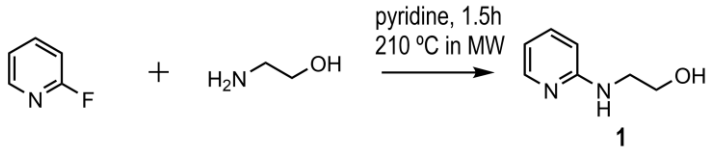
The synthesis of the thermolabile ligand **2** was done in two steps (**Scheme 4**).



Scheme 4. Retrosynthesis of the thermolabile ligand **2**.

5.1.1. SYNTHESIS OF N-(PYRIDIN-2-YL)-2-AMINOETHANOL (1)

Firstly, the synthesis of *N*-(pyridin-2-yl)-2-aminoethanol was carried out using commercially available reagents 2-fluoropyridine and 2-aminoethanol in pyridine (**Scheme 5**). The amine is attached to the pyridine via an aromatic nucleophilic substitution were the solvent acts as a base to form pyridium fluoride as a by-product. This reaction was assisted via MW in a sealed tube due to the need of high temperatures. [11]



Scheme 5. Synthesis of *N*-(pyridin-2-yl)-2-aminoethanol (**1**).

To separate the salt that was generated in the reaction, the number of extractions with aq. $NaHCO_3$ and EtOAc were reduced from the fifteen performed before to nine in order to minimize the loss of **1**. Besides, to remove the excess of 2-aminoethanol, extractions with sat. aq. NaCl were made. The average yield of this reaction was about 68%. Product **1** was characterized by ^{1}H-NMR spectroscopy (**Figure 4**), where pyridine aromatic protons are found from 6.5 ppm as multiplets due to ortho/meta/para couplings and the methylene protons appear as multiplets between 3 ppm and 4 ppm. The secondary amine proton can be easily identified by its broad signal close to 5 ppm.

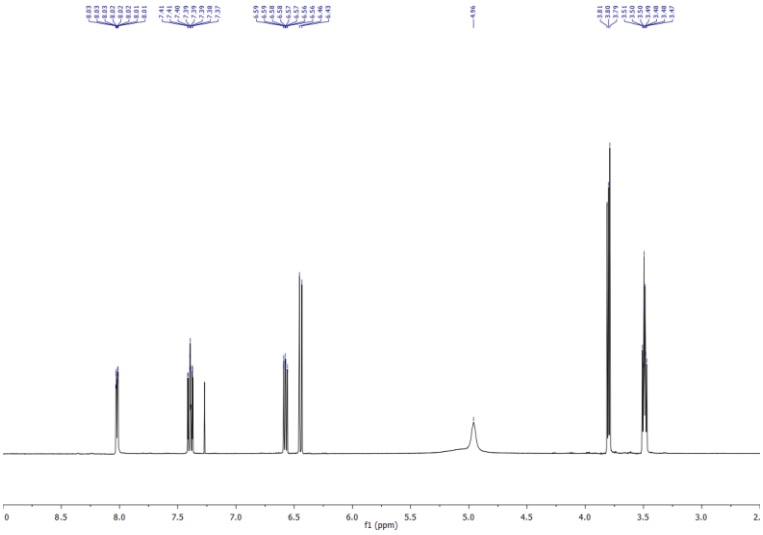


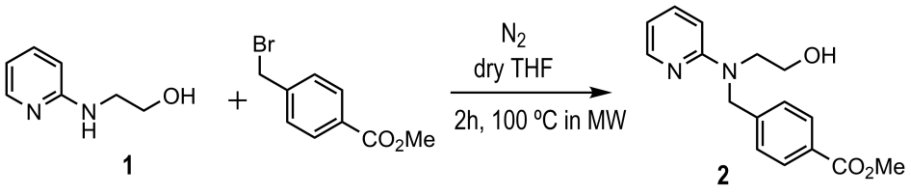
Figure 4. ^{1}H-NMR of product **1**.

5.1.2. SYNTHESIS OF 2

The synthesis of precursor **2** was performed from the product **1** through a nucleophilic substitution at a benzylic position using an excess of methyl 4-(bromomethyl)benzoate (**Scheme 6**). [12] The reaction is done under MW using dry THF as solvent and DIPEA as base.[13]

MW absorption is difficult when THF is used due to its low polarity. To increase the effectiveness of the process, tetrabutilamonium bromide was added to the mixture. The salt

increases the polarity of the medium and, as a result, the solution reaches the temperature required easily.



Scheme 6. Synthesis of methyl 4-[*N*-(2-hydroxyethyl)-*N*-(pyridin-2-yl)aminomethyl] benzoate (**2**).

To isolate the product **2**, some extractions with water were made to remove the salt from the reaction mixture. Then, the product was purified by column chromatography and the excess of methyl 4-(bromomethyl)benzoate was recuperated for further use. The final average yield was 54%. Product **2** was characterized by ^{1}H-NMR (**Figure 5**).

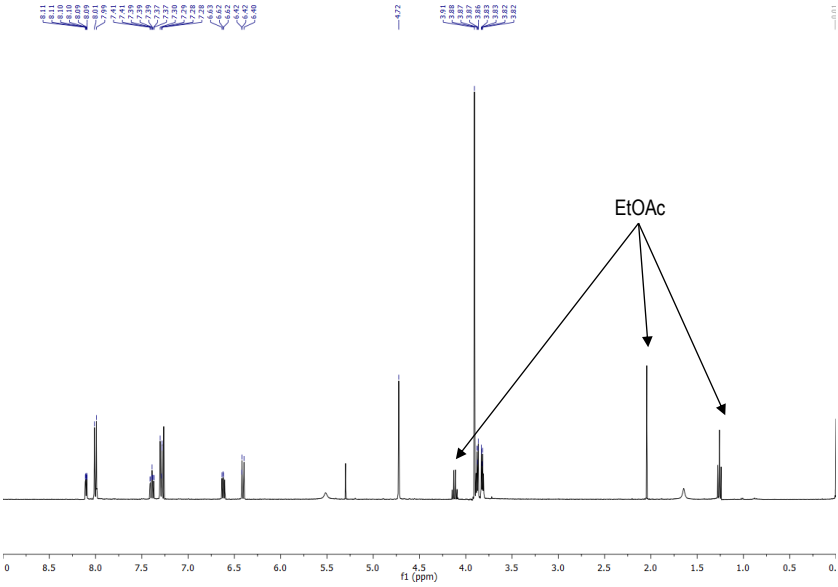
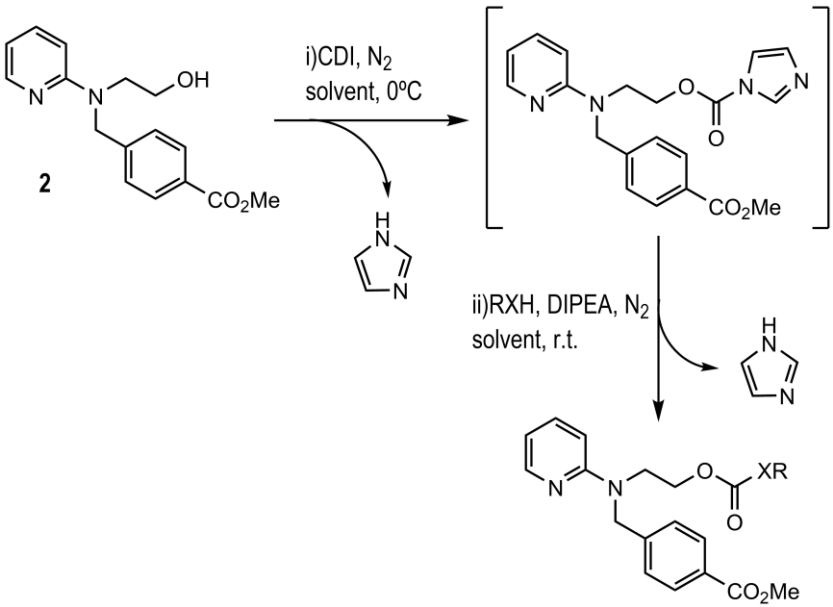


Figure 5. ^{1}H-NMR of product **2**.

New signals appeared due to the 4-mehtoxycarbonylbenzyl group, such as two doublets between 7 ppm and 8 ppm corresponding to the aromatic ring, two singlets between 3.5 ppm ad 5 ppm corresponding to benzylic methylene and methyl groups, and two triplets between 3.5 ppm and 4.0 ppm corresponding to the two aliphatic methylene groups.

5.2. SYNTHESIS OF THE CARBAMATES AND CARBONATES DERIVATES

The synthesis of the carbamate/carbonate derivatives were made in a one-pot two-step process using DCM as solvent. The first one was using the suitable amine/alcohol and CDI as the coupling agent with the precursor **2** in N_2 atmosphere because of the instability of CDI in a moisture environment. The second step was adding the amine/alcohol to the solution, also under inert atmosphere (**Scheme 7**).[14] DIPEA was used as the base in this step and the reaction was controlled by TLC.

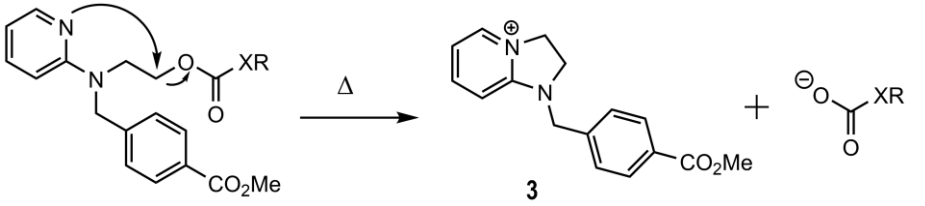


Scheme 7. Synthesis of carbonates and carbamates. X can be O or NH.

5.2.1. CARBAMATES

As an example of carbamate, it was decided to use glycine methyl ester hydrochloride. The analysis of the crude product by ^{1}H-NMR showed total conversion of **2** but no evidence of the desired product was detected. Instead, the NMR spectrum showed the peaks of the species

resulting from intramolecular cyclization (**Scheme 8**). These peaks (**Figure 4**) were assigned by the previous studies of Aida.



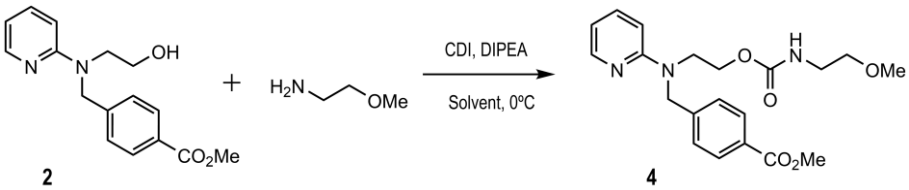
Scheme 8. Mechanism of cyclization and molecule's release. X can be O (carbonate) or N (carbamte).

Figure 6. Benzylic ^{1}H-NMR zone peaks of the cation 1-(4-(methoxycarbonyl)benzyl)-2,3-dihydro-1H-imidazo[1,2-a]pyridin-4-ium (**3**) resulting from cyclization of a carbonate or carbamate.

Pyridine peaks ^{a}H and ^{c}H and the benzylic ^{f}H from **2** appear to be deshielded in the spectrum compared to the non-cyclic molecule (**2**) because of the delocalized positive charge in the pyridine ring (**Figure 6**).

This carbamate was dismissed due to its unexpected instability at room temperature.

The second amine chosen was the commercially available 2-methoxyethylamine (**Scheme 9**).



Scheme 9. Synthesis of *N*-[4-(methoxycarbonyl)benzyl)-*N*-(pyridin-2-yl)amino]ethyl-2-methoxyethylcarbamate (**4**).

For this reaction, three syntheses were performed in different conditions (**Table 1**).

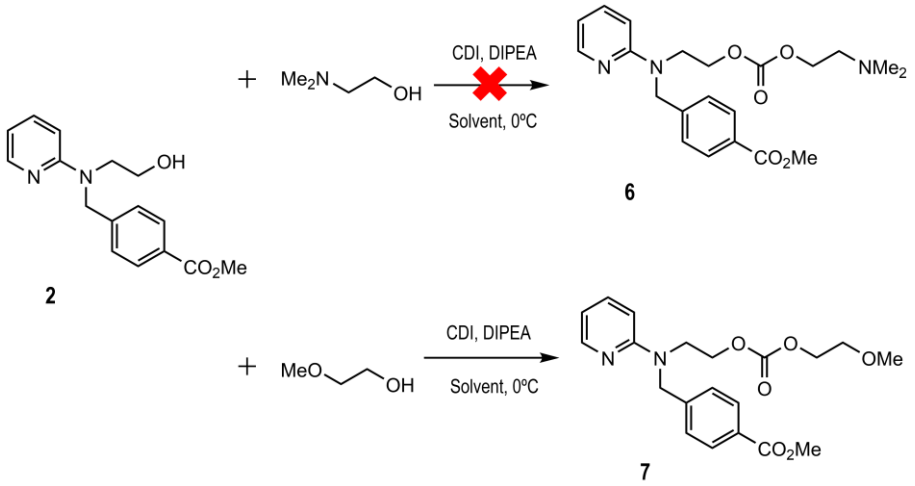
Entry	Solvent	Equiv of base	Equiv of amine	Time	Conversion (%)	Carbamate synthesized (%)
1	DCM	0	1	3h	69	33
2	DCM	1.5	1.5	3h	100	23
3	DCM	1.5	1.5	2.5h	92	22

Table 1. Reaction conditions of **4**.

Firstly, the reaction was tried without DIPEA (entry 1), but the ^{1}H-NMR crude showed traces of the cation **3** and **2**. Then, another synthesis increasing the number of equivalents of base and amine was made to guarantee the conversion of the reagents (entry 2). The spectrum showed a total reaction conversion of **2**, but there was a mixture 1.6 to 1 of the cation **3** and the desired carbamate. In order to reduce the amount of the former, a third synthesis was made with slow addition of the amine (entry 3). The ^{1}H-NMR showed a lower conversion of **2** and the resulting carbamate **4** was purified by column chromatography with a final yield of 16%.

5.2.2. CARBONATES

The same protocol that was used to prepare carbamates was followed for the synthesis of carbonates. The commercial alcohol precursors 2-dimethylaminoethanol and 2-methoxyethanol were chosen as simple models (**Scheme 10**).



Scheme 10. Synthesis of 2-dimethylaminoethyl [(4-(ethoxycarbonyl)benzyl)(pyridin-2-yl)amino]ethyl carbonate (**6**) and (*N*-[4-(methoxycarbonyl)benzyl](pyridin-2-yl)amino]ethyl 2-methoxyethyl carbonate (**7**).

In the case of 2-dimethylaminoethanol, three different assays were made in order to try to obtain the final product.

The time for the reaction of the alcohol with the activated derivative of **2** was changed to overnight so as to have a higher conversion to the desired product.

Entry	Solvent	Equiv of base	Equiv of alcohol	Equiv of CDI	Time (step 1/step 2)
1	DCM[(a)]	2	1	1	1h/Overnight
2	DCM[(b)]	2	1	1.5	3h/Overnight
3	ACN	1.5	1	1.8	3h/Overnight

Table 2. Reaction conditions for synthesis of **6**. (a) commercial; (b) distilled over CaH_2.

The crude of entry 1 was analysed by TLC and four different spots were observed. The ^{1}H-NMR showed that conversion of **2** was complete but a 45% of the cationic species coming from cyclization was detected. Purification by chromatography was made and three different fractions were collected, but none of them were the desired carbonate. The first fraction showed an unknown apparently pure compound that had the specific set of signals: quadruplet at 4.15 ppm and triplet at 4.36 ppm in a ratio 1.5 to 1. The other two fractions were **2** and an unknown mixture of products. It was speculated that the unknown product could be the ethyl carbonate resulting from reaction of the active intermediate with ethanol contained in the commercial DCM.

On account of overcoming this drawback and trying to obtain the desired carbonate, some experimental parameters were changed. For example, the CDI hydrolysis to imidazole due to environment humidity was detected by ^{1}H-NMR, which showed a 20% of decomposition. Seeing that, the reagent was used and stored from then under nitrogen atmosphere and the number of equivalents of CDI was increased to carry out the reaction. Moreover, it was decided to use DCM distilled over calcium hydride instead of the commercial one (entry 2). Once more, three fractions were isolated by column chromatography. The first one, was the unknown compound that gave triplet and quadruplet signals in the ^{1}H-NMR spectrum, and the other two fractions corresponded to product **2** recovered with a global percentage of 4.7%.

Owing to the DCM impurities, it was decided to change the solvent for the reaction. Thus, other studies proposed the synthesis of carbonates and carbamates using different solvents, like for example ACN.[14] Therefore, the synthesis was repeated in this solvent (entry 3). The crude was analysed by ^{1}H-NMR and a change of colour was noticed from dark orange to dark brown. The ^{1}H-NMR analysis showed that the compound had cyclized in a 93% and no starting **2** was detected. Some washings were made with H_2O in order to remove the salt corresponding to the cationic species **3** to find the source of the solution's colour. The crude resulting from the organic layer had a brownish colour and no product **6** was detected by ^{1}H-NMR analysis.

The synthesis of the second carbonate, (*N*-[4-(methoxycarbonyl)benzyl](pyridin-2-yl)aminoethyl 2-methoxyethyl-carbonate (**7**), was assayed under similar conditions to those described for carbonate **6** (**Table 3** and **Scheme 9**). In this case, after TLC analysis of the crude of both assays two fractions were obtained.

Entry	Solvent	Equiv of base	Equiv of alcohol	Equiv of CDI	Time (step 1/ step 2)
1	DCM	2	1	1	3h/Overnight
2	ACN	2	1	1.8	3h/Overnight

Table 3. Reaction conditions for synthesis of **7**.

When DCM was used as solvent (entry 1), the first fraction showed the same signals (triplet and quadruplet) of the unknown product detected when was tried the synthesis of carbonate **6**. Mass spectroscopy was done to the second fraction since **7** was apparently detected by ^{1}H-NMR due to a new set of benzylic signals, all together with other impurities. The mass spectrum showed a signal at m/z 389 corresponding to the $[M+H]^+$ of the desired carbonate, and a signal at 269 to the cationic species **3** (**Figure 7**).

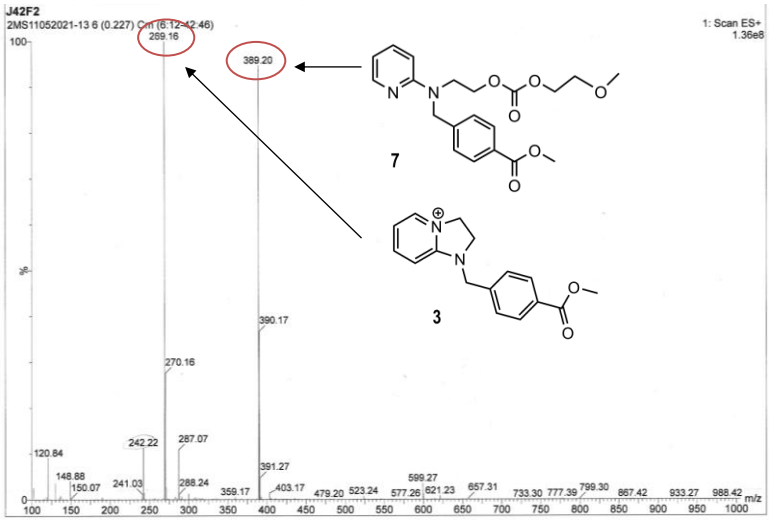


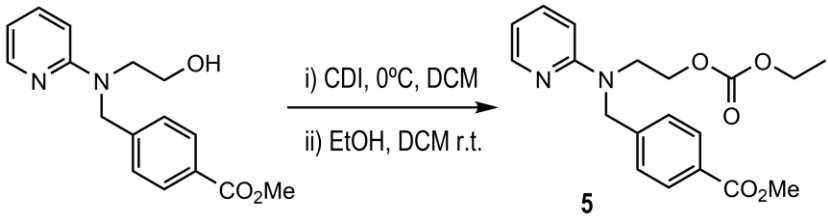
Figure 7. Mass spectrum of the second chromatographic fraction from the crude of the synthesis of **7** in DCM.

To isolate the carbonate, the fraction was purified by column chromatography. Because of the low mass of the sample, a single fraction was obtained even though different compounds were seen by TLC. The fraction was analysed by ^{1}H-NMR and mass spectroscopy and the

carbonate was not detected; an impurity had been isolated and the carbonate was lost during the column chromatography.

The synthesis was repeated using ACN (entry 2), the resulting crude was chromatographed and also two fractions were isolated. The first fraction corresponded to **2** and the second fraction (78,1mg) corresponded to the desired product **7**, as was demonstrated by ^{1}H-NMR and mass spectra analyses, together with small quantities of impurities in a ratio 1:1.08, determined by the areas of the signals corresponding to benzylic protons. Due to a lack of time, fraction two of entry 2 was not purified. Nevertheless, carbonate derivate **7** form 2-methoxyethanol could be synthesized and characterized by ^{1}H-NMR following the disappearance of the corresponding signals when heated to form the cyclized adduct **3**.

Furthermore, as to identify the first fraction of the unknown product of the synthesis of carbonates **6** and **7**, mass spectroscopy was done for both assays to prepare **6** (entries 1 and 2 of **Table 3**). The same results were obtained for the two samples, that is, a base peak m/z 359 and another peak at 269, corresponding to the cationic species **3**. The unknown peak at m/z 359 matched the $[M+H]^+$ ion for de unsymmetrical carbonate from **2** and ethanol. Therefore, the hypothesis that the solvent's impurity could have reacted with the reaction intermediate was plausible (**Scheme 11**).



Scheme 11. Reaction of ethanol with compound **2** mediated by CDI to give the carbonate **5**.

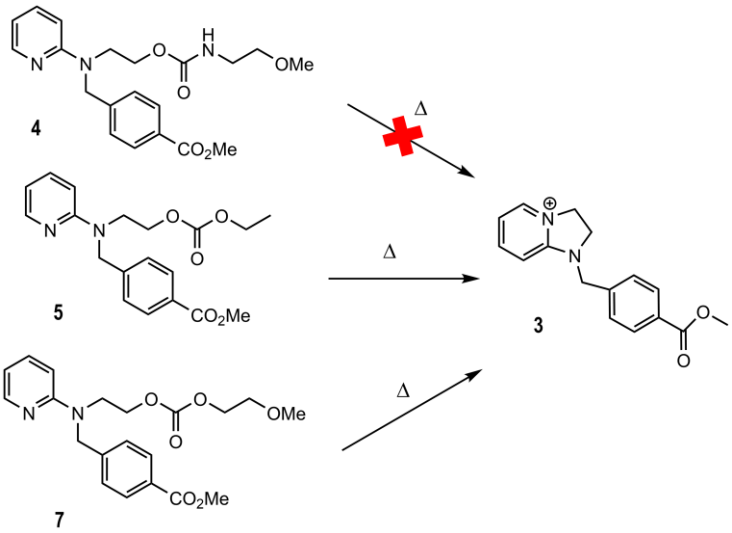
In order to prove this hypothesis, a synthesis of **5** was done following the same protocol. The ^{1}H-NMR analysis showed the same signals that were observed for the product isolated in the synthesis of carbonates **6** and **7** (Appendix 2). The reaction crude was purified by chromatography to give the expected carbonate **5** in a 21% yield.

Besides, to compare the different solvents that were used in terms of suitability to carry out the CDI mediated reactions, three reaction simulations were done without the compound **2** with

commercial DCM, anhydrous DCM and ACN (Appendix 5). For the two commercial DCM, small amounts of the carbonate **5** were detected by ^{1}H-NMR as well as other by-products, the cationic species **3** among them. When ACN was used, conversion of **2** to **3** was almost quantitative. The ethyl carbonate derivative **5** was not detected when reactions were performed to give carbamates, which could be due to the higher nucleophilicity of the amine than the alcohol (the first reaction step is performed at 0 °C while the second at room temperature). For ACN, probably due to the higher polarity of the solvent, it seems that cyclization takes place more easily. In conclusion, neither of the three solvents are suitable under these reaction conditions. Experiments done recently to prepare other carbonates using a DCM of analytical quality have given much better results in terms of the quality of the reaction crudes.

5.3. CYCLIZATION STUDIES

The thermal stability of the carbamate and the two carbonates synthesized were studied by means of ^{1}H-NMR experiments at different temperatures.



Scheme 12. Thermal decomposition of compounds **4**, **5** and **7**.

The carbamate **4** proved to be stable at rt and cyclization was not observed nor even at 80 ºC for more than an hour in each temperature. Concerning to carbonates, the cyclization of **5** was not observed after heating the carbonate at 60 ºC for 14 hours and 76% of cycled product **3** was detected when heated for 72h at 60ºC, as determined comparing signal areas of the carbonate and the cationic species (**Figure 8**). Clear evidences of the resulting products from decomposition of **5** are, for example, the doublet at 8.8 ppm corresponding to the aromatic proton close to the positively charged nitrogen of **3**, and the quadruplet at 3.7 ppm corresponding to the methylene protons of ethanol. For the carbonate **7**, cyclization was faster than in **5**, at rt there was already traces of **3** (8%). After 3h at 60 ºC there was 34% of **3** and, after 33h at the same temperature, the cyclization was complete (**Figure 9**). In this particular case, ^{1}H-NMR shows, apart from the signals corresponding to **3**, two triplets at 3.5 and 3.7 ppm corresponding to the two methylene groups of 2-methoxyethanol released during the decomposition process (Appendix 4).

It has to be mentioned that during the thermal treatment and in other assays performed at room temperature, a change to a dark brown colour could be observed probably due to the formation of cathodic species **3**.

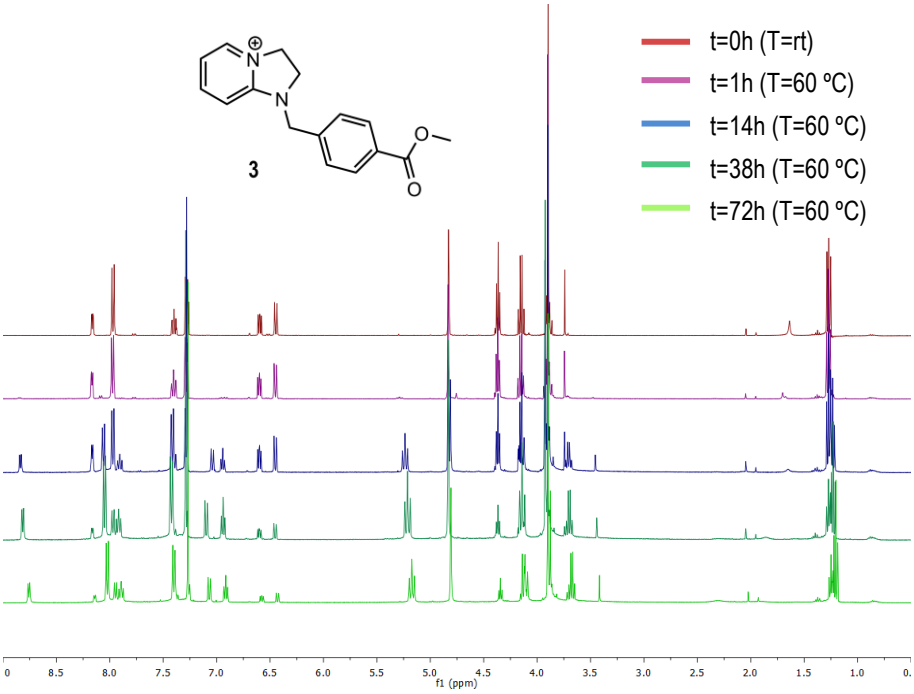


Figure 8. Decomposition process of **5** (t = time, T= temperature)

Two conclusions can be drawn from these assays. Firstly, carbamates are much more stable than carbonates, Thus, if carbamate **4** is compared with carbonate **7**, both compounds share the same 2-methoxyethyl group. Concerning to carbonates, carbonate **7** is less stable than carbonate **5**. Thus, the former had completely decomposed after 33h at 60 °C, while a 34% of **5** remained under the same conditions. A possible reason for this different behaviour could be the electron withdrawing effect of the methoxy group of **7** that destabilizes the carbonate.

Due to these results and others achieved in the laboratory, carbamates have been discarded for further studies and now the attention is focussing on reducing the stability of carbonates.

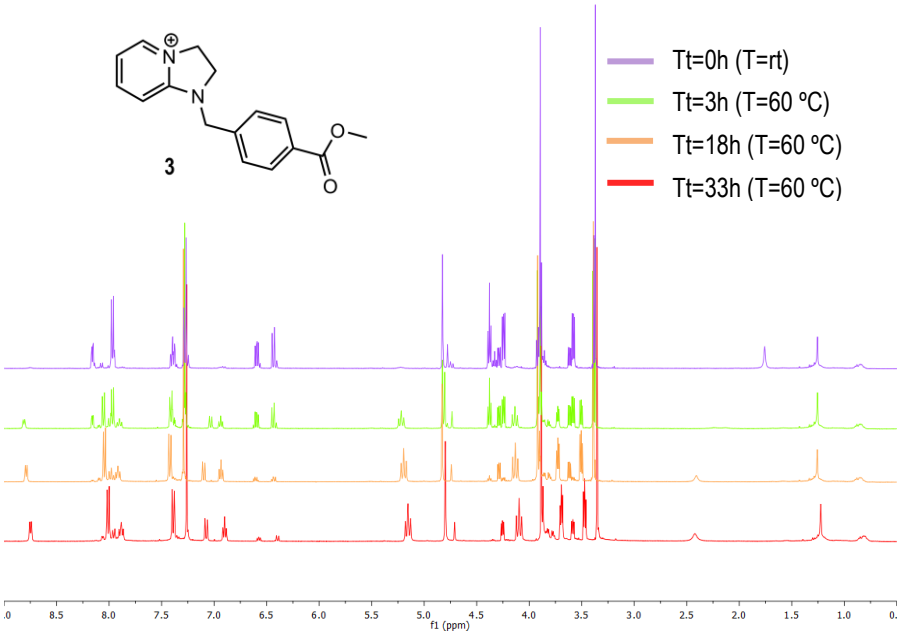


Figure 9. Cyclization process of 1-methoxyethyl [(4-(ethoxycarbonyl)benzyl)(pyridin-2-yl)amino]ethyl carbonate (**7**) (t = time, T= temperature).

6. EXPERIMENTAL SECTION

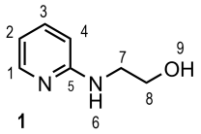
6.1. MATERIALS AND METHODS

Entry	Instrument	Brand	Model
1	Microwave	Biotage	Initiator Microwave System
2	Analytical balance	Mettler	Toledo AB254
3	HPLC-MS	Waters	LC-20AD
4	Rotatory evaporator	BUCHI	R-200
5	Ultra-sonic bath	P-Selecta	Ultrasons UB-1488
6	ESI-TOF	Applied Biosystems	4700 Proteomics
7	Masses exactes	Agilent	LC MSD TOF
8	IR Spectroscopy	Nicolet	6700 FT-IR

6.2. PREPARATION OF CARBAMATES AND CARBONATES DERIVATES

6.2.1. *N*-(pyridin-2-y)laminoethanol (1)

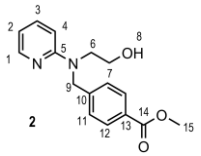
2-Fluoropyridine (1.44 mL, 17 mmol) and 2-aminoethanol (9.18 mL, 152 mmol) were dissolved in pyridine (4.5mL, 54 mmol) in a 20 mL MW vial. The mixture was stirred under MW irradiation for 1.5h at 210 ºC and let cool down. The solvent was evaporated under vacuum with toluene (5 x 20 mL) as it makes an azeotrope with pyridine and helps to remove it from the solution. Sat aq. NaHCO3 (20 mL) was added to the mixture and the two phases were separated. The aqueous layer was washed with EtOAc (9 x 20 mL), organic layers were combined and washed with sat aq. NaCl (2 x 20 mL). The resulting organic solution was dried with anh. MgSO4 and concentred under reduced pressure to afford the desired product **1** as a pale yellow oil that crystallises as a white solid. The final yield was 73%.



Yellow oil. IR (film): 3292, 3145, 3029, 2852, 1605, 1521, 1452, 1057, 984 cm-1 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (ddd, J = 5.2, 1.9, 0.9 Hz, 1H, H^1), 7.39 (ddd, J = 8.5, 7.1, 1.9 Hz, 1H, H^3), 6.58 (ddd, J = 7.1, 5.2, 0.9 Hz, 1H, H^2), 6.44 (dt, J = 8.4, 0.9 Hz, 1H, H^4), 4.96 (s, 2H, H^6, H^9), 3.84 – 3.77 (m, 2H, H^7), 3.49 (q, J = 5.4, 4.2 Hz, 2H, H^8). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.8 (C^5), 147.2 (C^1), 137.6 (C^3), 113.1 (C^2), 108.5 (C^4), 63.5 (C^8), 45.5 (C^7). HRMS (+ESI): *m/z* requires for $C_7H_{11}N_2O$ $[M+H]^+$ 139.0872; found 139.0863.

6.2.2. Methyl 4-[*N*-(2-hydroxyethyl)-*N*-(pyridin-2-yl)aminomethyl]benzoate (2)

Under N_2 atmosphere, Compound **1** (600 mg, 4.3 mmol) and methyl 4-(bromomethyl)benzoate (600 mg, 4.35 mmol) were dissolved in dry THF (8 mL). Next, were added tetrabutilamoniumbromide (250 mg, 8.7 mmol) and DIPEA (2 mL, 20.89 mmol). The mixture was stirred under MW for 2h at 100 ºC and then, let cool down until rt. The solvent was evaporated under reduced pressure and the resulting crude was suspended in EtOAc (20 mL) and washed with water (2 x 20 mL) to remove the salts. Then, the solvent was removed under reduced pressure to afford an oil that was chromatographed on silica-gel employing DCM:EtOAc (2:1) as eluent. The desired product was obtained as a yellow oil in a 55% yield (686.9 mg),and starting product **1** (10%) was recovered as a white solid.

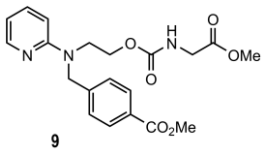


Yellow oil. IR (ATR): 3371, 2948, 1715, 1593, 1488, 1433, 1273, 1106, 769 cm-1 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (ddd, J = 5.1, 2.0, 0.9 Hz, 1H, H^1), 8.00 (d, J = 8.3 Hz, 2H, H^{12}), 7.39 (ddd, J = 8.8, 7.1, 2.0 Hz, 1H, H^3), 7.31 – 7.27 (d, 2H, H^{11}), 6.65 – 6.59 (dd, 1H, H^2), 6.41 (d, J = 8.7, 0.9 Hz, 1H, H^4), 4.72 (s, 2H, H^9), 3.91 (s, 3H, H^{15}), 3.89 – 3.80 (m, 4H, H^6, H^7). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.8 (C^{14}), 158.8 (C^5), 147.1 (C^1), 143.2 (C^{10}), 138.1 (C^3), 130.2 (C^{12}), 129.3 (C^{13}), 126.6 (C^{11}), 113.1 (C^2), 106.9 (C^4), 63.2 (C^6), 53.7 (C^9), 53.1 (C^7), 52.1 (C^{15}). HRMS (+ESI): *m/z* requires for $C_{16}H_{19}N_2O_3$ $[M+H]^+$ 287.1397; found 287.1382.

6.2.3. *N*-[4-(methoxycarbonyl)benzyl)-*N*-(pyridin-2-yl)amino]ethyl-*N*-(2-methyl ethanoate) carbamate (9).

In a 10 mL round bottomed flask, **2** (288 mg, 1.06 mmol) was dissolved in commercial DCM (2.5 mL) under N_2 atmosphere. The solution was slowly added to a 25 mL two-neck round bottomed flask with CDI (142 mg, 0.88 mmol) dissolved in DCM (2.5 mL) under N_2 atmosphere. The mixture was stirred at rt for 1 h when glycine methyl ester hydrochloride (109 mg 0.87 mmol)

and DIPEA (0.25 mL, 1.44 mmol) were slowly added to the reaction mixture. The solution was stirred overnight at rt and volatiles were removed under reduced pressure. The resulting crude showed by ^{1}H-NMR the signals corresponding to the cyclized species and H-Gly-OMe.



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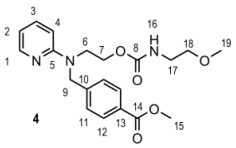
6.2.4. *N*-[4-(methoxycarbonyl)benzyl)-*N*-(pyridin-2-yl)amino]ethyl 2-methoxyethyl-carbamate (4).

In a 10 mL round bottomed flask **2** (152 mg, 0.53 mmol) was dissolved in DCM (2.5 mL) under N_2 atmosphere. The solution was slowly added to a 25 mL two-neck round bottomed flask with CDI (85 mg, 0.52 mmol) dissolved in DCM (2.5 mL) under N_2 atmosphere. The mixture was stirred for at rt for 1 h when 2-methoxyethylamine (59 mg 0.79mmol) and DIPEA were slowly added to the reaction mixture. The solution was stirred overnight at rt and volatiles were removed under reduced pressure. The resulting crude was purified by column chromatography using DCM:EtOAc (2:1) and product **4** was isolated as a brown oil. The final yield was 16%.



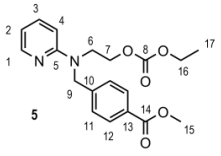
4

Brown oil. IR (ATR): 3342, 2926, 1713, 1594, 1530, 1270, 1016, 977, 769 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 – 8.13 (ddd, 1H, H^1), 7.99 – 7.94 (d, 2H, H^{12}), 7.40 (ddd, J = 1.7 Hz, 1H, H^3), 7.28 (d, J = 8.6 Hz, 2H, H^{11}), 6.58 (dd, J = 7.1, 4.9, 0.8 Hz, 1H, H^2), 6.48 (d, J = 8.7, 0.9 Hz, 1H, H^4), 4.94 (s, 1H, H^{16}), 4.83 (s, 2H, H^9), 4.28 (t, J = 5.9 Hz, 2H, H^7), 3.89 (s, 3H, H^{15}), 3.83 (t, J = 5.8 Hz, 2H, H^6), 3.43 – 3.29 (m, 7H, H^{17}, H^{18} i H^{19}).^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.9 (C^{14}), 157.8 (C^5), 156.3 (C^8), 148.0 (C^1), 144.3 (C^{10}), 137.4 (C^3), 129.9 (C^{12}), 128.9 (C^{13}), 126.7 (C^{11}), 112.5 (C^2), 105.9 (C^4), 71.3 (C^{18}), 62.5 (C^7), 58.7 (C^{19}), 52.5 (C^9), 52.0 (C^{15}), 47.9 (C^6), 40.7 (C^{17}). HRMS (+ESI): *m/z* requires for $C_{20}H_{25}N_3NaO_5^+$ $[M+Na]^+$ 410.1693; found 410.1689. *m/z* requires for $C_{20}H_{26}N_3O_5^+$ $[M+H]^+$ 388.1874; found 388.1865.

6.2.5. Ethyl *N*-[4-(methoxycarbonyl)benzyl]-*N*-(pyridin-2-yl)aminoethyl carbonate (5).

In a 10 mL round bottomed flask **2** (172 mg, 0.60 mmol) was dissolved in DCM (2.5 mL) under N_2 atmosphere. The solution was slowly added to a 25 mL two-neck round bottomed flask with CDI (196 mg, 1.2 mmol) dissolved in commercial DCM (2.5 mL) under N_2 atmosphere. The

mixture was stirred at rt for 1.5h when ethanol (28 mg, 0.61 mmol) and DIPEA were slowly added to the reaction mixture. The solution was stirred overnight at rt and volatiles were removed under reduced pressure. The resulting crude was purified by column chromatography on silica-gel using DCM:EtOAc (2:1) as eluent, yielding 45 mg (21%) of **5** as a yellow oil and a small fraction of **2** was recovered.



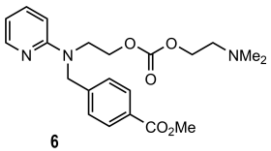
Brown oil. IR (ATR): 3399, 2925, 1742, 1717, 1648, 1488, 1255, 1107, 769 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 8.16 (ddd, J = 4.1, 1.1 Hz, 1H, H^1), 7.99 – 7.95 (m, 2H, H^{12}), 7.40 (ddd, J = 8.6, 7.1, 2.0 Hz, 1H, H^3), 7.28 (d, J = 8.8 Hz, 2H, H^{11}), 6.60 (ddd, J = 7.2, 4.9, 0.8 Hz, 1H, H^2), 6.45 (dt, J = 8.6, 0.9 Hz, 1H, H^4), 4.83 (s, 2H, H^9), 4.36 (t, J = 5.9 Hz, 2H H^7), 4.15 (q, J = 7.2 Hz, 2H, H^{16}), 3.95 – 3.86 (m, H^{15} i H^6), 1.27 (t, J = 7.1 Hz, 3H, H^{17}).^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.9 (C^{14}), 157.7 (C^8), 155.1 (C^5), 148.0 (C^1), 144.0 (C^{10}), 137.5 (C^3), 130.0 (C^{12}), 129.0 (C^{13}), 126.6 (C^{11}), 112.7 (C^2), 106.0 (C^4), 65.59 (C^7), 64.08 (C^{16}), 52.74 (C^9), 52.06 (C^{15}), 47.55 (C^6), 14.24 (C^{17}). HRMS (+ESI): *m/z* requires for $C_{19}H_{23}N_2O_5$ $[M+H]^+$ 359.1608; found 359.1597.

6.2.6. 2-dimethylaminoethyl [(4-(ethoxycarbonyl)benzyl)(pyridin-2-yl)amino]ethyl carbonate (6).

In a 10 mL round bottomed flask, **2** (**Table 4**) was dissolved in DCM (2.5 mL) under N_2 atmosphere. The solution was slowly added to a 25 mL two-neck round bottomed flask with CDI (**Table 4**) dissolved in solvent (2.5 mL, **Table 4**) under N_2 atmosphere. The mixture was stirred at rt for 1.5h when 2-dimethylaminoethanol (**Table 4**) and DIPEA (0.24 mL, 1.38 mmol) were slowly added to the reaction mixture. The solution was stirred overnight at rt and volatiles were removed under reduced pressure. The resulting crude chromatographied on silica-gel using DCM:EtOAc (2:1) but product **6** was not detected in any of the fractions that were collected.

Entry	Solvent	2 (mg / mmol)	CDI (mg / mmol)	2-dimethylaminoethanol (mg / mmol)
1	DCM[(a)]	188 / 0.66	129 / 0.80	62 / 0.69
2	DCM[(b)]	197 / 0.69	165 / 1.0	63 / 0.71
3	ACN	216 / 0.75	277 / 1.7	68 / 0.76

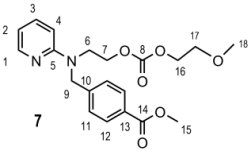
Table 4. Reaction conditions for synthesis of **6**. (a) commercial; (b) distilled over CaH_2.



6

6.2.7. (*N*-[4-(methoxycarbonyl)benzyl](pyridin-2-yl)amino]ethyl 2-methoxyethyl-carbonate (7).

In a 10 mL round bottomed flask **2** (0.194 g, 0.67 mmol) was dissolved in DCM (2.5 mL) under N_2 atmosphere. The solution was slowly added to a 25 mL two-neck round bottomed flask with CDI (0.196 g, 1.0 mmol) dissolved in commercial DCM (2.5 mL) under N_2 atmosphere. The mixture was stirred at rt for 3h when 2-methoxyethanol (0.053 g 0.69 mmol) and DIPEA were slowly added to the reaction mixture. The solution was stirred overnight at rt and volatiles were removed under reduced pressure. The resulting crude was purified by column chromatography on silica-gel using DCM:EtOAc (9:1) as eluent, affording 78 mg of product **7** as an slightly impurified yellow oil.



7

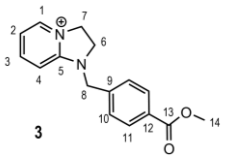
Brown oil. IR (ATR): 2951, 1743, 1716, 1594, 1488, 1434, 1256, 1106, 788, 769, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (ddd, J = 5.0, 1.9, 0.9 Hz, 1H, H^1), 7.99 – 7.94 (d, 2H, H^{12}), 7.43 – 7.35 (ddd, 1H, H^3), 7.29 – 7.25 (d, 2H, H^{11}), 6.59 (ddd, J = 7.1, 4.9, 0.8 Hz, 1H, H^2), 6.44 (dt, J = 8.7, 0.9 Hz, 1H, H^4), 4.83 (s, 2H, H^9), 4.38 (t, J = 5.9 Hz, 2H, H^7), 4.26 – 4.21 (m, 2H, H^{16}), 3.95 – 3.83 (m, 5H, H^6 i H^{15}), 3.60 – 3.55 (m, 2H, H^{17}), 3.38 (d, J = 5.2 Hz, 3H, H^{18}).^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.9 (C^{14}), 157.7 (C^5), 155.1 (C^8), 148.03 (C^1), 144.0 (C^{10}), 137.5 (C^3), 130.0 (C^{12}), 129.0 (C^{13}), 126.6 (C^{11}), 112.74 (C^2), 106.0 (C^4), 70.16 (C^{17}), 66.91 (C^{16}), 65.92 (C^7), 59.01 (C^{18}), 52.78 (C^9), 52.06 (C^{15}), 47.52 (C^6). LRMS (m/z +ES): $C_{20}H_{24}N_2O_6^+$ $[M+H]^+$ requires 388.1, found 389.20.

6.2.10. Cyclization studies

The cyclization studies of **4**, **5**, and **7**, were performed in the NMR tube using $CDCl_3$ as solvent. The compound **4** was heated for 1 h at 50 ºC, 60 ºC and 80 ºC, but no cyclization was observed. For the carbonate **5**, some cyclization was detected at rt before heating the sample (8% of **3**). The carbonate was heated for at 60 ºC and spectra were registered at different times: 3h (34% of cyclization), 18 h (96% of cyclization) and 33h (quantitative cyclization). Finally, for the

carbonate **7**, the sample was heated at 60 ºC for 1h (no cyclization was observed), 14 h (43% of cyclization), 38 h (75% of cyclization) and 72 h (76% of cyclization).

The cycled molecule could be characterized easily due to the total conversion of carbonate **5**



3

^{1}H NMR ($CDCl_3$, 400 MHz): 8.75 (d, J = 6.4 Hz, 1H, H^1), 8.03 – 7.98 (d, 2H, H^{11}), 7.88 (t, 1H, H^3), 7.41 – 7.32 (d, 2H, H^{10}), 7.08 (d, J = 8.9 Hz, 1H, H^4), 6.90 (t, J = 6.8 Hz, 1H, H^2), 5.15 (t, J = 9.9 Hz, 2H, H^7), 4.80 (s, 2H, H^8), 4.10 (t, J = 9.9 Hz, 2H, H^6), 3.88 (s, 3H, H^{14}). LRMS (m/z +ES): $C_{16}H_{17}N_2O_2^+$ $[M+H]^+$ requires 269.0, found 269.1.

10. CONCLUSIONS

The synthesis of the thermolabile ligand methyl 4-[*N*-(2-hydroxyethyl)-*N*-(pyridin-2-yl)aminomethyl]benzoate (**2**) was been carried out in two steps with moderate global yields (52-54%) after chromatographic purification.

Compound **2** was used to synthesize the 2-methoxyethylcarbamate from 2-methoxyethylamine (**4**), and the ethyl and 2-methoxyethyl carbonates from ethanol (**5**) and 2-methoxyethanol (**7**) respectively. Reactions were carried out in a two-step one-pot protocol using CDI for carbonylatiion. Yields were 16%-21% after chromatographic purification. All products synthesized in this work (**1**, **2**, **4**, **5**, and **7**) were characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and LRMS or HRMS spectrometry.

The synthesis of the carbamate from glycine methyl ester was tried under similar conditions but the product could not be isolated due to its instability at rt, affording the products resulting from the intramolecular cyclization. On the other hand, The synthesis of the carbonate from 2-dimethylaminoethanol was also tried under different conditions, that is, changing the amounts of CDI or the base and the solvent (DCM or ACN). Unfortunately, the product could not be isolated in none of the assays that were carried out.

Commercial DCM proved to be unsuitable to perform reactions with CDI. Thus, the small quantities of EtOH contained in the solvent afforded the corresponding carbonate as a by-product of the reaction. On the other hand, the reaction done in ACN afforded more than a 90% of intramolecular cyclization, probably due to a polarity higher that DCM that favours the undesired process.

The thermal stability of carbamate **4** and carbonates **5** and **7** were assayed. The carbamate resulted to be more stable than carbonates. Thus, the carbamate proved to be stable even at 80 ºC for 1 h. However, both carbonates were unstable at 60 °C, affording the pyridinium salt and the corresponding alcohol resulting from intramolecular cyclization. Carbonate **7** resulted to be more unstable than carbonate **5** because cyclization was completed after 33h at 60 ºC for the former while a 76% of the latter remained after 72h at the same temperature.

11. REFERENCES AND NOTES

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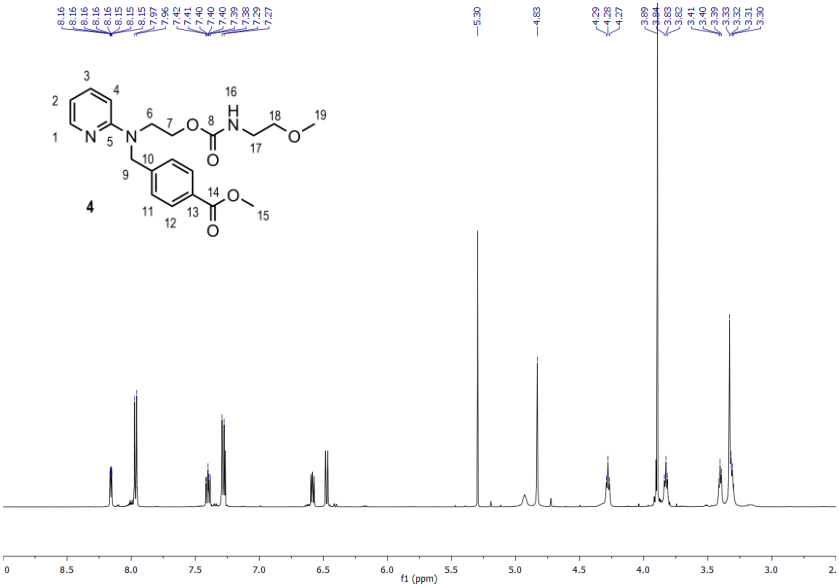
12. ACRONYMS

TPGs	Thermolabile protecting groups
NMR	Nuclear Magnetic Resonance
DDS	Drug Delivery Systems
CDI	1,1'-Carbonyldiimidazole
MNP	Magnetic nanoparticle
MW	Microwave
THF	Tetrahydrofuran
r.t.	Room temperature
TLC	Thin-layer chromatography
DCM	Dichloromethane
DIPEA	N,N-diisopropylethylamine
EtOAc	Ethyl acetate
ACN	Acetonitrile
ATR	Attenuated total reflection
HPLC-MS	High-Pressure Liquid Chromatography-Mass Spectrometry
IR	Infrared Spectroscopy
LRMS	Low Resolution Mass Spectroscopy
HRMS	High Resolution Mass Spectroscopy

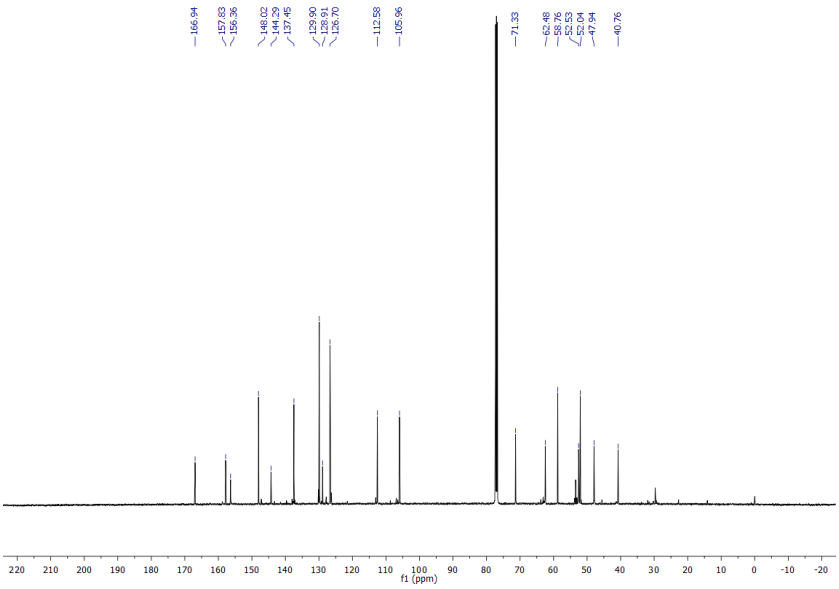
APPENDICES

APPENDIX 1: SPECTRAL DATA OF CARBAMATE 4

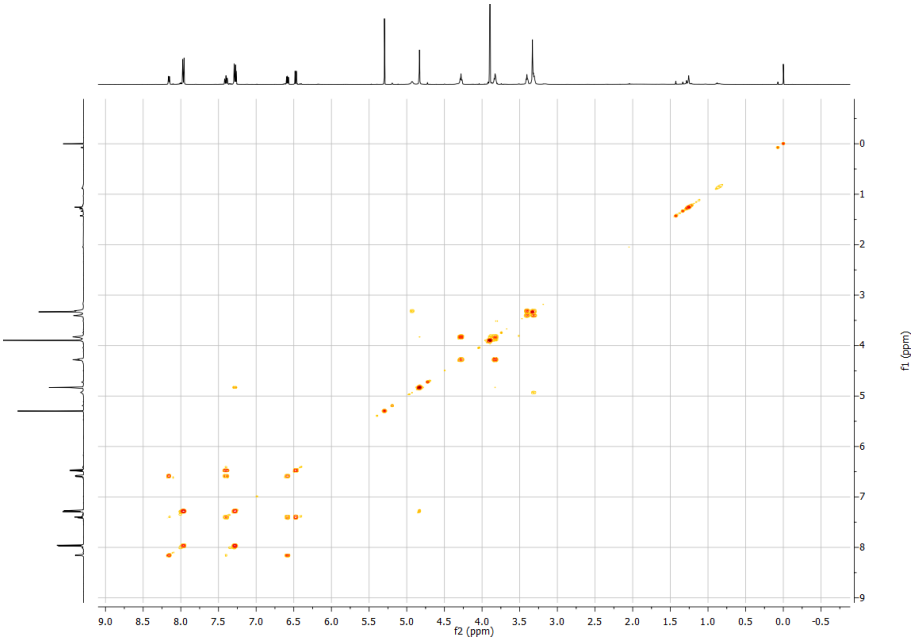
^{1}H-NMR of **4**



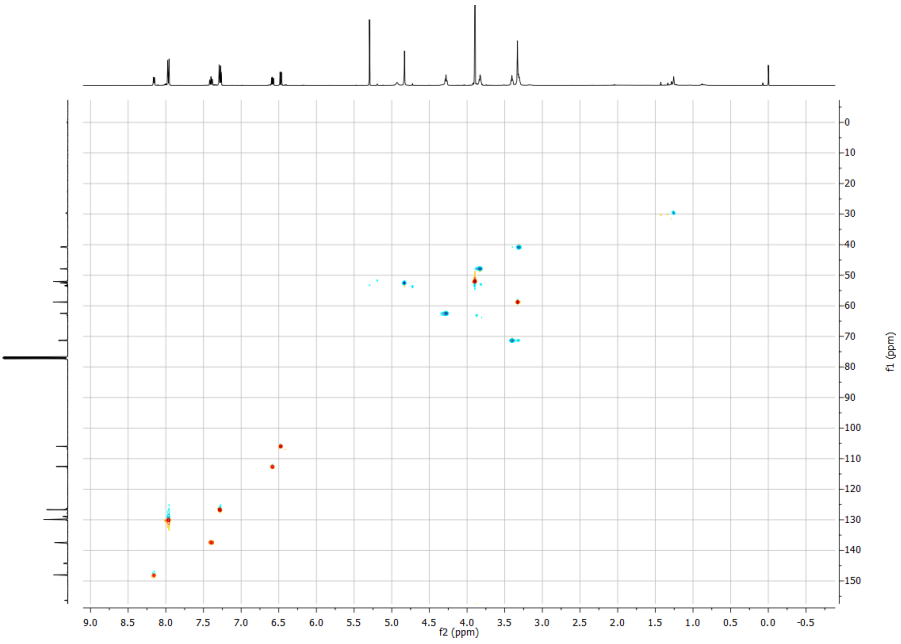
^{13}C-NMR of **4**



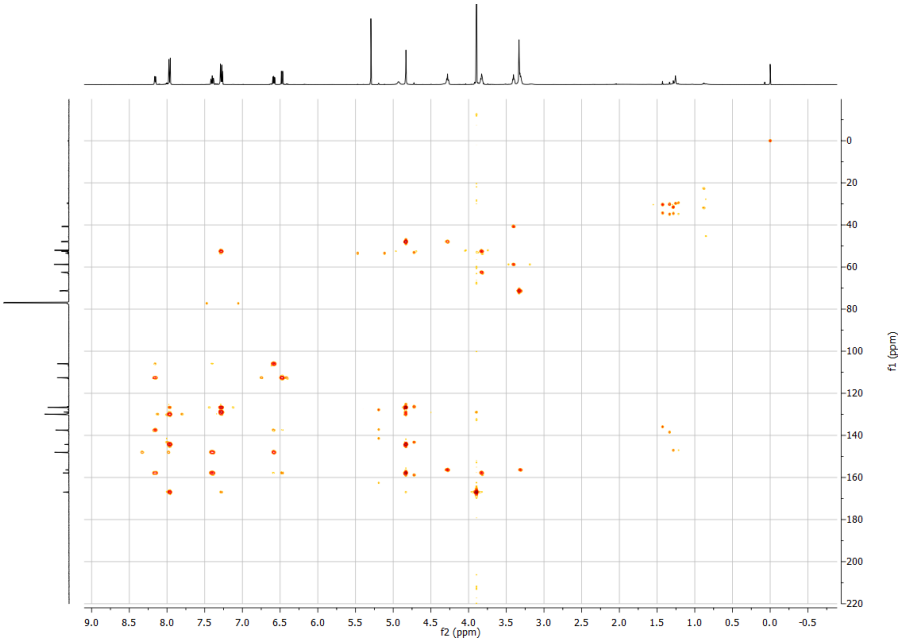
COSY NMR of **4**



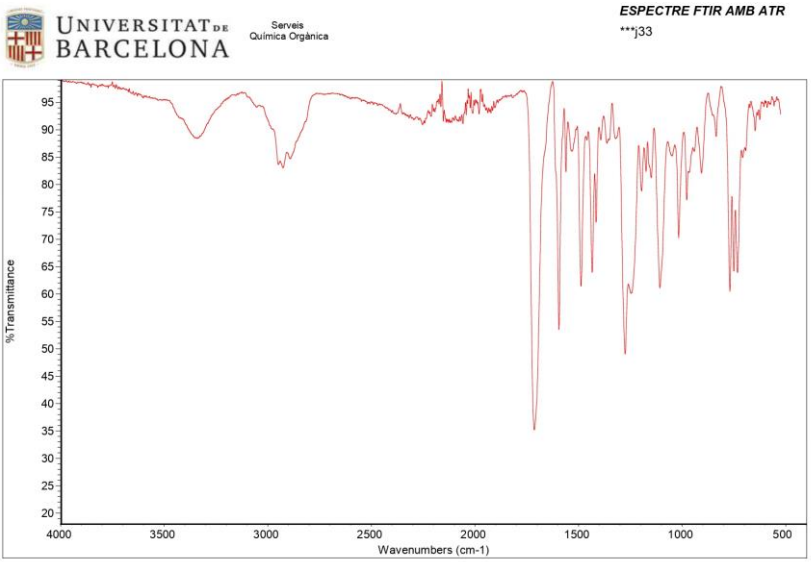
HSQC NMR of **4**



HSQC NMR of **4**

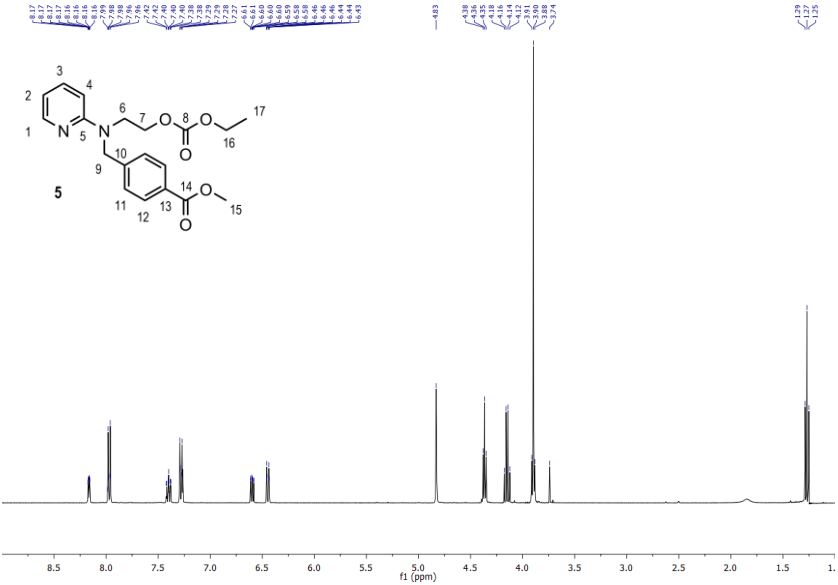


IR Spectra of **4**

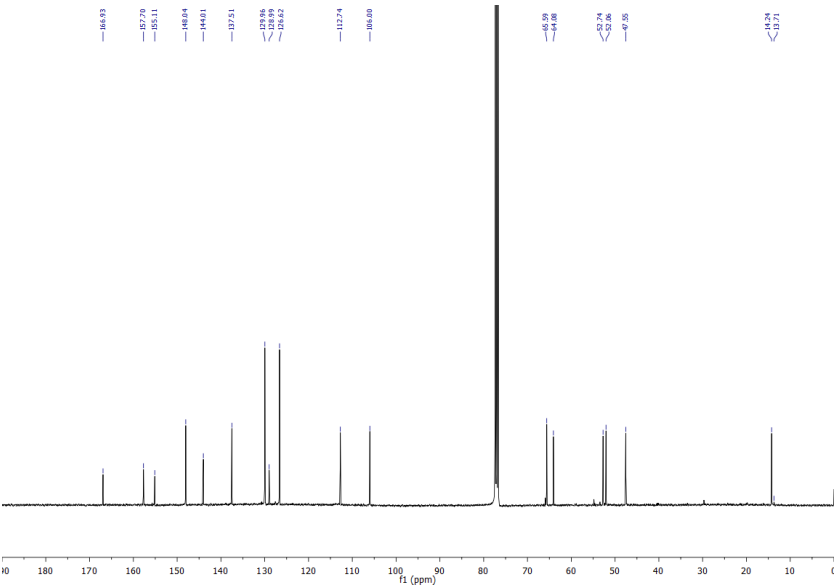


APPENDIX 2: SPECTRAL DATA OF CARBONATE 5

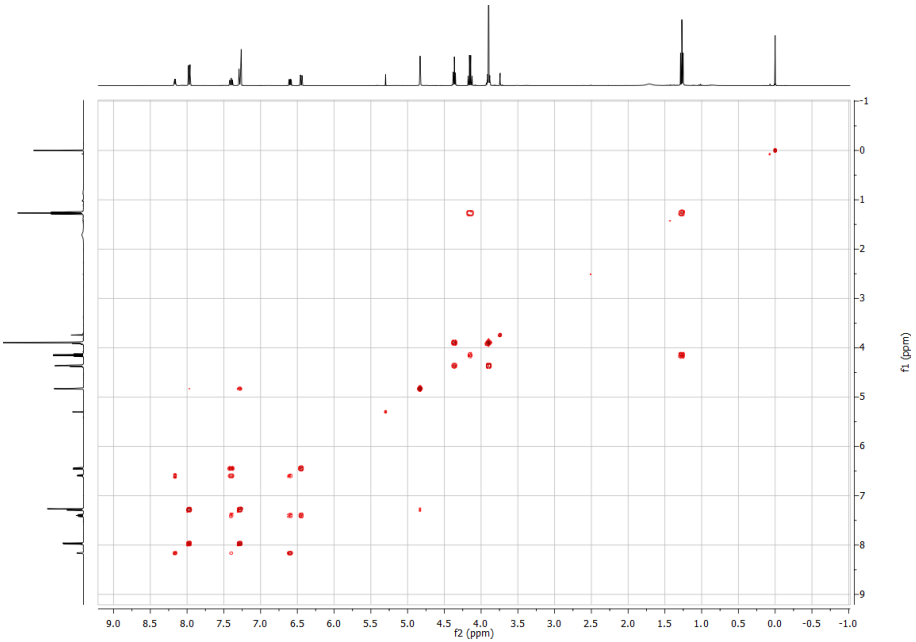
^{1}H-NMR of **5**



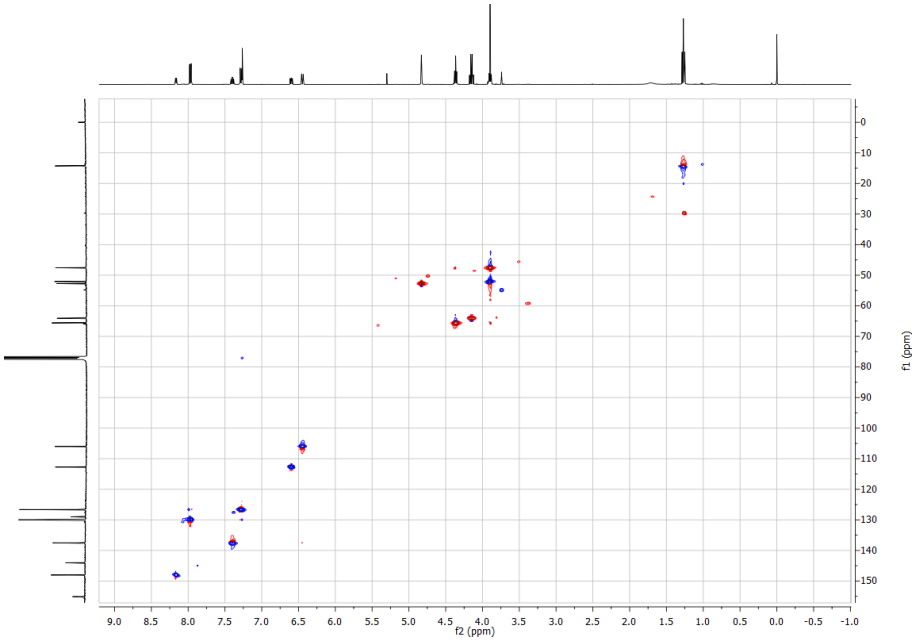
^{13}C-NMR of **5**



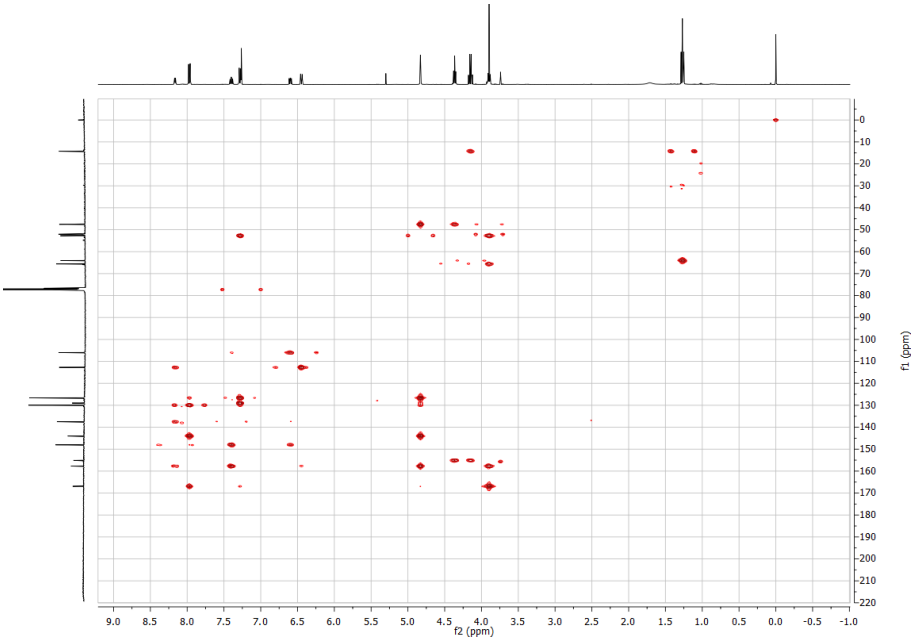
COSY NMR of **5**



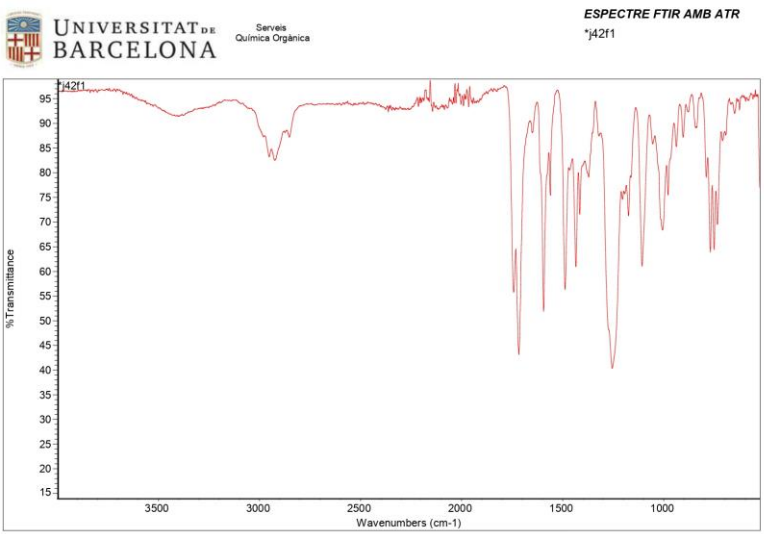
COSY NMR of **4**



HMBC NMR of **5**

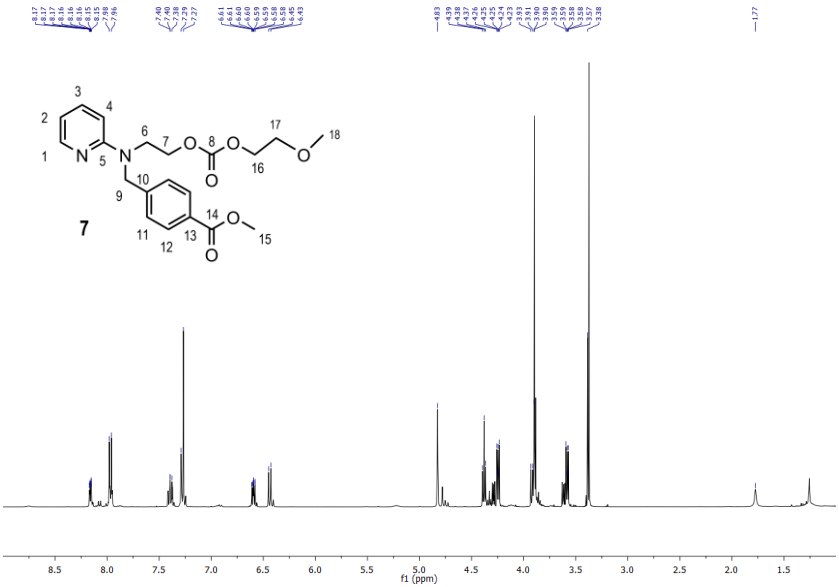


IR Spectra of **5**

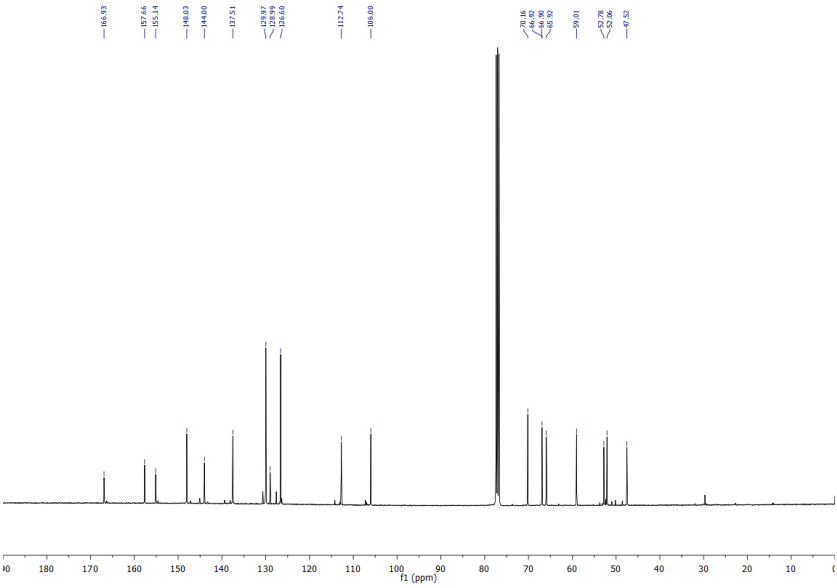


APPENDIX 3: SPECTRAL DATA OF CARBONATE 7

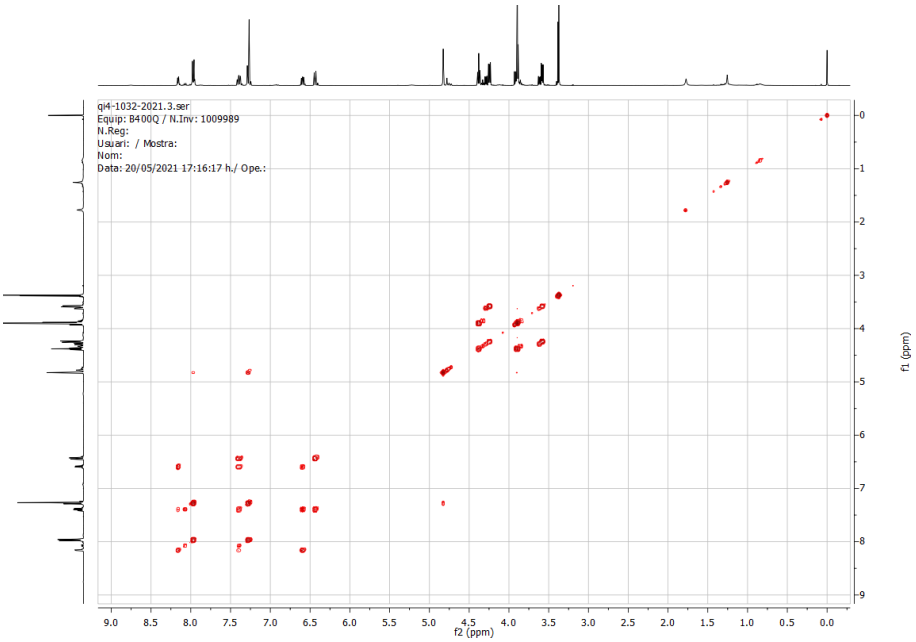
^{1}H-NMR of **7**



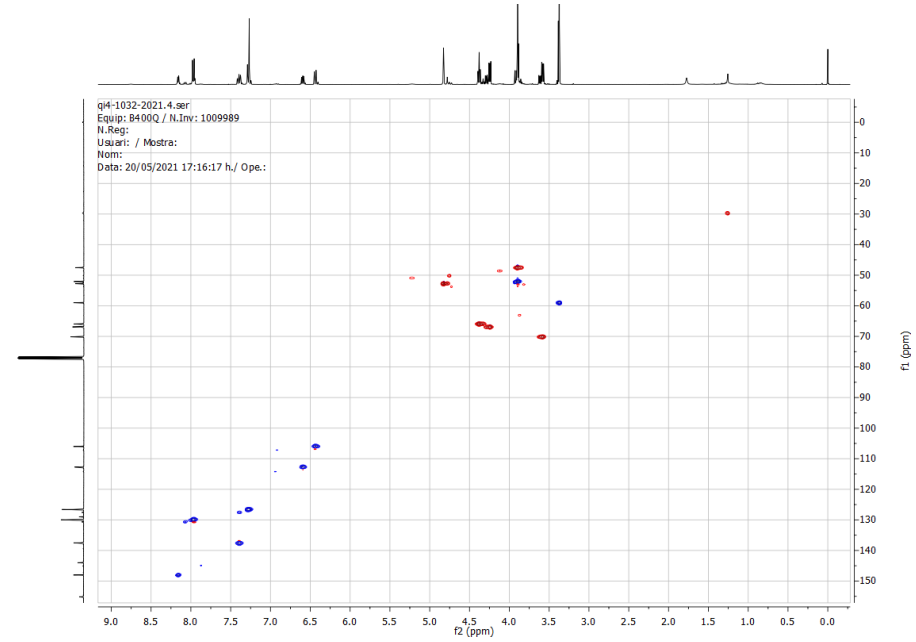
^{13}C-NMR of **7**



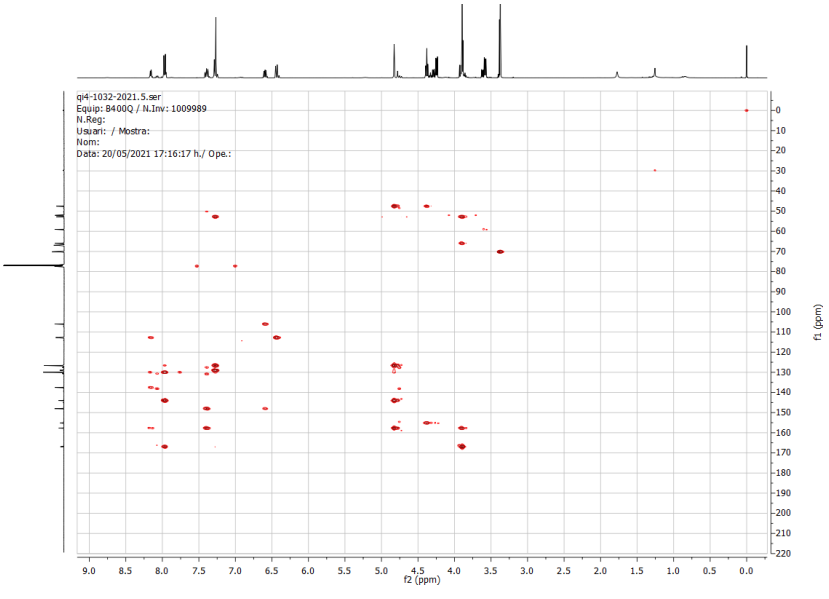
COSY NMR of **4**



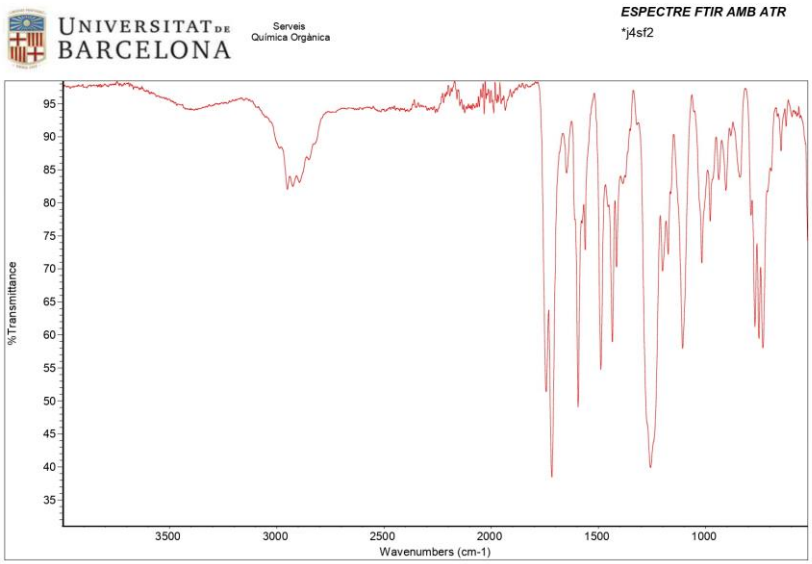
HSQC NMR of **7**



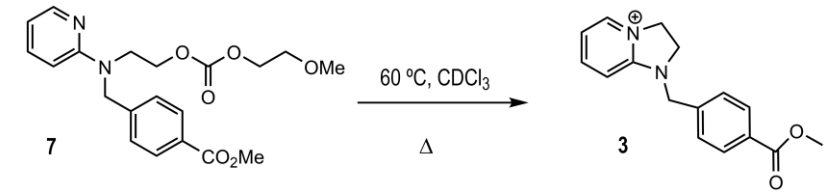
HMBC NMR of **7**

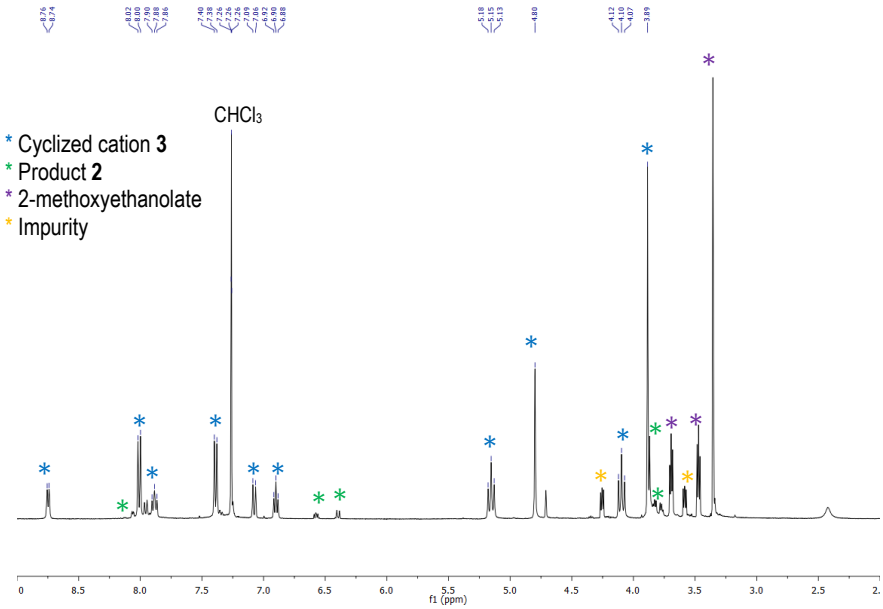


IR Spectra of **7**



APPENDIX 4: SPECTRAL DATA OF CARBONATE AFTER 33 H AT 60 ºC (3)





APPENDIX 5: 1H-NMR SPECTRA OF CRUDE MATERIALS RESULTING FROM MIXING 2 WITH CDI IN DIFFERENT SOLVENTS UNDER STANDARD CONDITIONS FOR CARBONATE/CARBAMATE SYNTHESIS.