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by

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Halide-free synthesis of *N*-aryl carbamate

Research group: Catalysis and green chemistry (CatLab)

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Tiivistelmä – Referat – Abstract

Carbamates have been an attractive topic for a long time. Due to their wide range of applications, especially in agriculture, medicine and pharmacy. Three general synthesis methods have been in use, i.e. via phosgene, via isocyanate and the reaction with carbon dioxide. Since the first two processes include highly toxic phosgene and slightly less toxic isocyanate, they are less preferable. Recently, the interest has grown towards reaction with CO_2, due to its nontoxicity and environmentally safer use.

The focus of this thesis was a preparation of *N*-aryl carbamates through halide-free pathway. The optimization reactions were done in two steps under catalytic conditions with several different parameters, such as temperature, catalysts and time of reaction. The first step represents a reaction between carbonate and aromatic amine, forming a carbamate intermediate under nucleophilic conditions. In the second step, the intermediate reacts further with an alcohol to form the final carbamate product under basic conditions. Usual waste in the carbamate synthesis *via* phosgene are ammonia, halide acids or other alkyl halides. Due to their toxicity and harmful environmental effects, they represent a group of compounds that are not desirable to obtain from the reactions. Since the introduced procedure avoids the usual formation of toxic halide acids as the main waste product, and forming trifluoroethanol (TFE) instead, it represents an environmentally friendlier method.

In the experimental section, various optimization steps are studied for the syntheses of intermediate and product. The obtained results are not examined only qualitatively, but also quantitatively. Therefore, intermediate and product yields were analysed by GC-MS analytical method, ^{1}H NMR, ^{13}C NMR and FT-IR spectra.

Avainsanat – Nyckelord – Keywords
Carbamates, halide-free synthesis, catalytic reactions, phosgene, isocyanate, aromatic amines, alcohols, CO_2, carbonates

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Abbreviations

AA = amino alcohol

ACN = acetonitrile

Alloc = allyloxycarbonyl

Boc = *tert*-butoxycarbonyl

BTC = bis-(1,1,1-trichloromethyl) carbonate; triphosgene

Cbz = benzyloxycarbonyl

DABCO = 1,4-diazabicyclo[2.2.2]octane

DBC = dibutyl carbonate

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM = dichloromethane

DEC = diethyl carbonate

DMC = dimethyl carbonate

DMF = *N,N*-dimethylformamide

DPC = diphenyl carbonate

EtOAc = ethyl acetate

GC-MS = gas chromatography – mass spectroscopy

HDI = hexamethylene di-isocyanate

HPLC = high-performance liquid chromatography

IUPAC = International Union of Pure and Applied Chemistry

LA = Lewis acid

LB = Lewis base

MDI = methylene diphenyl di-isocyanate

MTO = mineral turpentine oil

NMR = nuclear magnetic resonance spectroscopy

PU = polyurethanes

RT = room temperature

TDI = toluene di-isocyanate

TFE = 2,2,2-trifluoroethanol

TLC = thin layer chromatography

TMG = 1,1,3,3-tetramethylguanidine

TMTU = 1,1,3,3-tetramethylthiourea

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1. Introduction

1.1 Carbamates

In the authority of IUPAC (International Union of Pure and Applied Chemistry), carbamates are considered as *N*-substituted esters or salts, derived from an unstable carbamic acid. They are organic compounds with a chemical structure $R^1OCONR^2R^3$, as shown in Figure 1. The R^1 functional group can be either alkyl, aryl or cation.[1] Therefore the alkyl carbamates consist of two parts; alkyl, which represents *O*-alkyl ester and carbamate, representing substituents on the nitrogen atom. Their primary categorization is divided into two classes, depending on the attached substituents in the structure. Organic carbamates represent a stable group of compounds, typically produced from amines and other molecules with attached carboxyl group, leading to relationship of O-CO-NH-.[2] Inorganic carbamates, on the other hand, appear for the groups with coupled metallic or nonmetallic atom.[3]

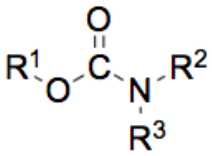


Figure 1. Chemical structure of carbamates.

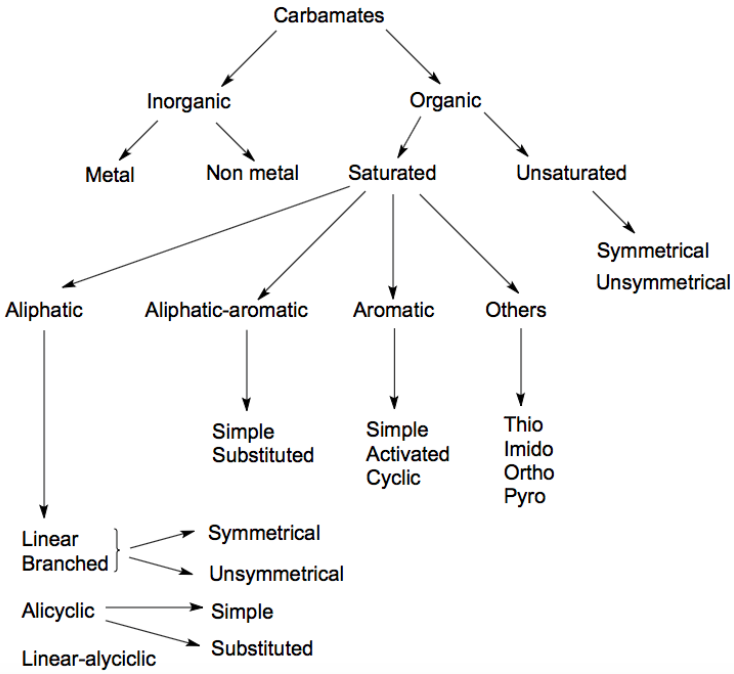


Figure 2. Classification of carbamates.

The very first carbamate formation might be assigned to Wohler's procedure in 1840, when he synthesized ethyl carbamate from urea and ethanol.[1] Since then, various procedures for carbamate formation have been developed, depending on the carbonyl source. Figure 3 shows the possible processes for *N*-substituted carbamates, according to different type of carbonyl source, such as phosgene, carbon monoxide, carbon dioxide, dimethyl carbonate and urea. Thus, practical procedures include amine phosgenation, reductive nitro and oxidative amine carbonylation, amine methoxycarbonylation, urea alcoholysis and direct reactions of CO, alcohol and amine.[4] However, the formation of cyclic carbamates from carbon dioxide utilization, requires electron-deficiency of the carbon atom in CO_2, which has been first reported in the aspirin synthesis by Hermann Kolbe and Rudolf Schmitt in 1860. The latter, i.e. the Kolbe-Schmitt reaction, has been discovered as the reaction of CO_2, which undergoes nucleophilic attack to form salicylic acid.[5]

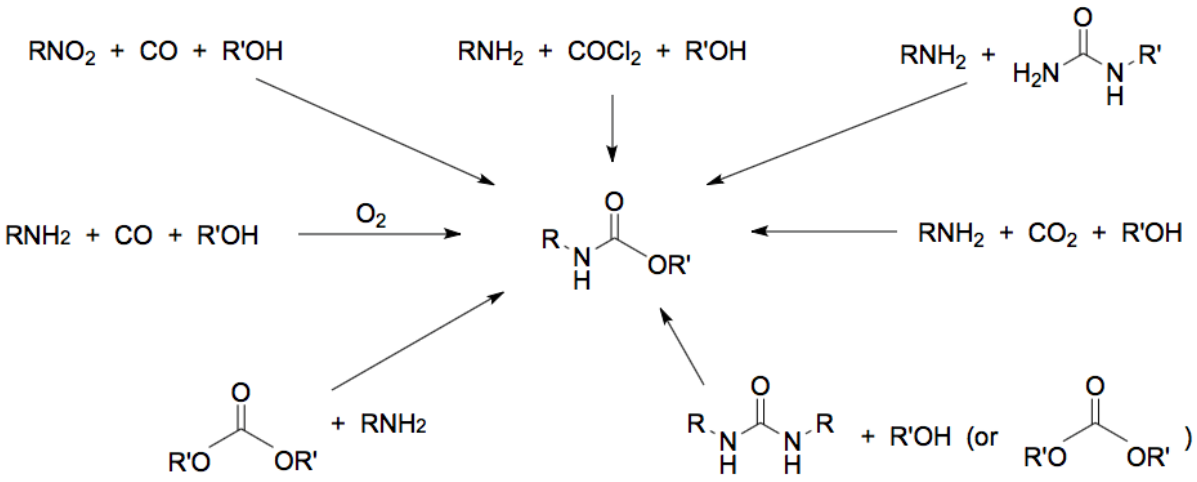


Figure 3. The processes of N-substituted carbamates synthesis with different carbonyl sources.

Carbamate derivatives have wide spectrum of applications. One of the important features is their use in agriculture, as pesticides, fungicides and insecticides.[6,7] The properties of the insecticides were first investigated in 1930's, while carbamate pesticides have been synthesized and commercially used since the 1950's and applied in various crops all around the world.[8] Along with organophosphorus compounds, they stand for the most common applied pesticides and a great replacement of poisonous organochloride pesticides since 1970's, even though they still show toxic properties.[9] Few of them, containing aromatic substituents, are assumed to be potentially carcinogenic and mutagenic. Moreover, they show acute toxicity for mammals and aquatic organisms.[10,11] However, they are not representing an issue just for the organisms, but also for the environment. With more than 10,000 tons of used carbamates in agriculture per year, their cleanup became highly prioritized.[12]

Furthermore, polyurethanes (PUs) represent another important carbamate feature, even though they are causing great environmental problems.[13] They were invented by German professor Dr. Otto Bayer and his co-workers[14], who discovered di-isocyanate poly- addition technique of the reaction between di-isocyanate and polyester diol, which started PU industry in 1937.[15,16] They are representing polymerized carbamate groups, also called urethanes. However, ethyl carbamate, also named urethane, is not a part of PU formation and therefore has no connection with PU in any way. Urethanes are commonly synthesized from an alcohol and an isocyanate, while carbamates are usually made from non-isocyanate pathway.[17] PU form materials with great structure – property correlations and own precise biological, chemical and physical features. Therefore, they have various applications, such as surface coatings, synthetic fibers, insulators, elastomers, foams, etc.[18], where the major use goes to packaging.[19] Additionally, they can be also used as protective groups for the amino groups, where the most convenient and frequent are *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and allyloxycarbonyl (Alloc).[1]

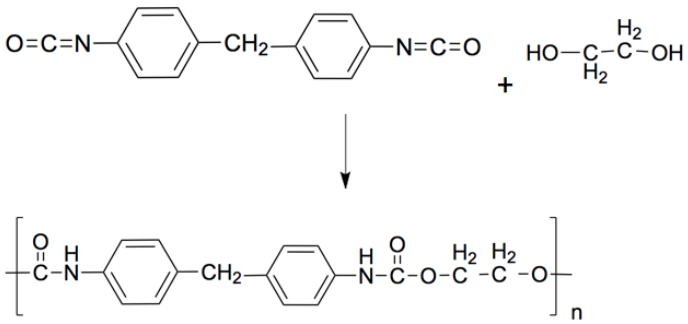


Figure 4. Common route for the synthesis of polyurethanes from di-isocyanate and polyol.[18]

As a starting material, carbamates have also a leading role in the paint industry.[20] When they are applied in medicine and pharmaceutical industry[6,7], their unique structure has a significant role in drug and prodrug designing. Hydrogen bonding within the carboxyl group and the backbone NH can modulate together biological properties, improve stability and pharmacokinetics, due to their substitution on the O- and N-termini. From amide-ester composition, they have a strong chemical stability and ability to modify inter- and intramolecular interactions.[21] As urethanes, they have been demonstrated in the role of various therapeutic agents. Especially five- or six-membered cyclic and bicyclic fused carbamates represent promising compounds in pharmaceutical field, due to their satisfying stability and normally not being subjected to the metabolic ring opening.[18] Therefore, cyclic carbamates has been studied as a potential HIV-1 protease (6-membered carbamate rings), as an antibiotic and as in possible cancer treatment (5-membered carbamate rings).[20] Carbamates stability is provided from the resonance between the amide and carboxyl group, which has been studied by estimation of the C-N bond rotational barriers.[22] Three resonance structures, achieved from carbamate stabilization, are shown in the Figure 5.

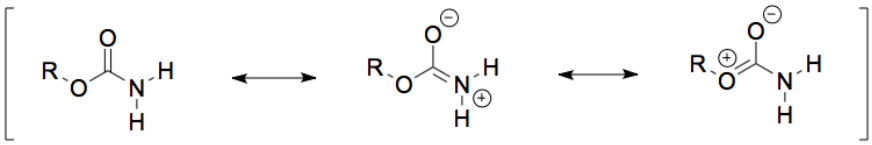


Figure 5. The carbamate moiety structures of the resonance.

Another important feature is referred to their conformation, containing *syn* and *anti* isomers, due to a pseudo double bond of the carbamate motifs.[23,24] *Anti* isomers has been shown as a preferable conformation, with the local minimum of an energy between 1.0−1.5 kcal mol^{-1}, while a mixture of 50:50 (*anti : syn)* has been detected, when the energy difference is almost zero. This represents the significance of carbamate low activation energy in the molecular devices.[23] R and R^1 substituents must be studied carefully in the both conformers (Figure 6), due to their influence on the free-energy difference between them. Therefore, steric effects and R^1 electronegativity must be considered.[25] Consequently, only *anti* conformers result in the five-, six- and seven-membered cyclic carbamates.

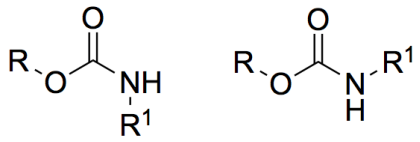


Figure 6. Syn (left) and anti (right) conformations of carbamates.[18]

Since chemical industry generates a wide range of toxic wastes, a large interest in reducing hazardous reagents and solvents has been applied. The approaches are mainly focused on product formation with high process productivity and elimination of perniciousness for the environment, such as halide acids. Therefore, formation of ionic liquids could be one of the strategies, since they are known as an important component of green solvents. Furthermore, they can be produced from halide-free one-pot synthesis, which is a promising method of reducing toxic solvents from the habitat. Since the main waste product of this thesis is 2,2,2-trifluoroethanol (TFE), it represents halide-free procedure, without any formation of toxic halide acids. Therefore, this work show promising and environmental friendly approach for further applications in chemistry and chemical industry.

2. Scope of the thesis

The focus of this thesis is a preparation of *N*-aryl carbamates through halide-free pathway in the optimized two-step reaction. Final review of this subject is assured up till August, 2018. For better understanding and knowledge of this work, an overview of the methods for carbamate synthesis is given. Since this work consists of an optimization study for catalytic reactions of carbonates with aromatic amines and alcohols, many different techniques have been additionally performed for the isolation of the final product, such as TLC and flash chromatography. However, those methods are not included, since they are not related to the core idea behind the experimental part of the thesis.

3. Literature review

3.1 Synthesis of carbamates in general

Carbamate syntheses have been successfully developed by many different methods. So far they have been prepared by Hofmann[26-28], Curtius and Lossen rearrangements[29,30], the carbonylation of nitroaromatics[31], the carbonylation of amines[32], the reaction of alcohols with isocyanates[33] and carbon dioxide alkylation.[34-37] Standard techniques mainly consist of synthesis including toxic phosgene and isocyanate. Therefore, methods can be divided into three general procedures; *via* phosgene (direct method), *via* isocyanate (indirect) and the reaction with carbon dioxide. Direct and indirect methods include phosgene as a starting material, which is known as a highly toxic compound. It is a multipurpose reagent in various synthesis of many organic compounds, which allows to construct building blocks of two nucleophilic units attached to both sides. Moreover, it is also useful for the synthesis of carbonates and ureas.[38] However, carbamates can be also formed directly from isocyanates, which appear as an intermediate in both methods. They are slightly less toxic compounds, but still undesirable due to their formation from the phosgene.

3.1.1 Features and toxicity of phosgene and isocyanate

As already mentioned in chapter 1, carbamates are presented as a promising core structure in the valuable pharmaceutical drugs, in agriculture and medicine. However, their preparation requests for hazardous or pricey reagents, i.e. phosgene or isocyanate.[39-42]

Phosgene, also called carbonyl chloride, is a colorless gas at the room temperature and pressure, first discovered by a chemist John Davy in the early 19th century. Nowadays it is formed from exothermic reaction of carbon monoxide and chlorine gas through the activated catalytic carbon.[43]

$$CO(g) + Cl_2(g) \longrightarrow COCl_2(g)$$

Figure 7. Phosgene formation from carbon monoxide and chlorine gas.

Most importantly, it is known as highly toxic gas, with its threshold limit value (TLV) 0.1 ppm and the lethal concentration (LC_{50}) of 340 ppm in 30 minutes for rat and 500 ppm in one minute for human, provided by ILO (International Labour Organization) and WHO (World Health Organization). Its most dangerous exposure route is by inhalation, causing sore throat, persistent coughing, chest pain, shortness of breath or even vomiting.[44] So far it has been largely used in the production of polyurethanes, pesticides, herbicides and dyes. Moreover, it was used as a chemical weapon during World War I (WWI).[45] Phosgene has been shown as a very versatile reagent, used for approaching acyl and alkyl chlorides.[46] In addition, as a dehydrating agent, it can result in cyanides, isocyanides and carbodiimides.

Another toxic compound used in the carbamate synthesis, is isocyanate. It refers to organic compounds with the chemical group -N=C=O, attached to alkyl or an aromatic ring. They are very reactive and have a small molar mass. As an electrophile, it reacts with many nucleophiles such as amines and alcohols. Therefore, reaction with an alcohol produces urethane bond.[47] Depending on the nucleophile, it gives various products along with many applications. If isocyanate contains hydroxyl groups, it forms polyurethanes. Upon water reaction, it forms carbon dioxide, while the reaction with amines produces ureas (shown in Figures 8, 9, 10).[48] Most commonly used compounds are di-isocyanates, such as methylene diphenyl di-isocyanate (MDI), toluene di-isocyanate (TDI) and hexamethylene di-isocyanate (HDI).

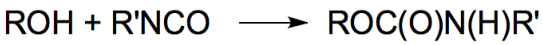


Figure 8. Formation of urethane linkage.[48]

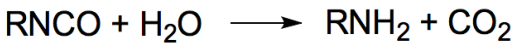


Figure 9. Formation of carbon dioxide.[48]

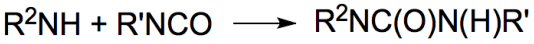


Figure 10. Formation of urea.[48]

Isocyanates can be also used as a manufacture of flexible and non-flexible foams, fibers, coatings, wood protection, etc. However, they are proved to have harmful effects on the health. Their small molar mass provides faster volatilization at the ambient temperature, creating toxic inhalation vapor. Upon their exposure, similarly to the phosgene, they cause skin irritation, chest tightness and difficult breathing, where the main consequence is asthma and additional lung problems. Furthermore, they are classified as carcinogens and mutagens compounds. The exposure reactions might occur either immediately (minutes after exposure), late (number of hours after) or dual (combination of both, immediately and late).[49] LD_{50} is normally couple of hundred milligrams per kilogram[50], while short-term exposure limit (STEL) is limited to extraordinarily low 0.07 mg/m^{-3} for almost all isocyanates.[51]

3.1.2 Catalytic reactions

Catalytic reactions have an extremely important role in the organic chemistry as a method of accelerating the chemical reaction rate by the additional substance called catalyst. Its general purpose is to change the reaction mechanism in a way of lowering the activation energy. Therefore, the catalyst forms a temporary intermediate, while not going under any chemical change.[52] Depending on the catalyst and reactant phase, the reaction can be divided in two groups, i.e. homogenous (both in the same phase) or heterogeneous (in the different phase). There are several ways to accelerate reactions by catalysts, such as increasing the electrophilicity, nucleophilicity or stability of transition state. Thus, four different types of catalysis may be employed, i.e. acid, base, nucleophilic and metal-ion catalysis.

This work is based on two-step reaction, starting as a nucleophilic catalytic reaction in the first step and continued as a base catalysis in the second step. Thus, those two types of catalysis will be explained in the following literature part.

Nucleophilic catalysis

Nucleophilic catalyst, also called Lewis base, is a very effective nucleophile and has a good leaving group characteristics. A free electron pair on the catalyst represents the main starting point of the catalytic reaction. Therefore, the Lewis base attacks the positive substrate moiety, usually carbon, and then the nucleophile attaches on it. Afterwards, the leaving group finally separates itself and leaves the molecule.[53] In general, nucleophilicity depends on the solvation energy of the nucleophile, strength of the electrophile-nucleophile chemical bond, steric hindrance, electronegativity of the nucleophile, etc. Moreover, solvents represent another important feature of nucleophilicity with a great effect on a reaction rate through hydrogen bonding.

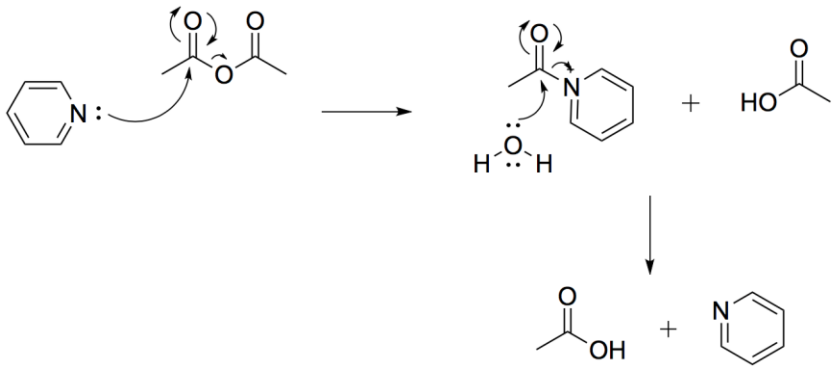


Figure 11. Mechanism of the nucleophilic covalent catalysis with the fast first step.

Base catalysis

Despite the fact, that basicity is a subgroup of nucleophilicity, they both represent different types of mechanisms. Therefore, nucleophiles are Lewis bases, which donate the electron pair and attack any atom, different than a hydrogen. On the other hand, Brønsted bases are present in base catalysis and form a bond with a proton. Also, nucleophilic reactions are usually irreversible and without an equilibrium[53], which is why the nucleophilicity determines the reaction rate. On the contrary, base catalysis are reversible and can be measured by the pK_a, which refers to base and conjugate acid position in the equilibrium.[54] The reaction pathway follows the base donation of an electron pair to a proton, where it attaches on the base, giving the molecule positive charge and leaving the previous compound with a negative charge (Figure 12).

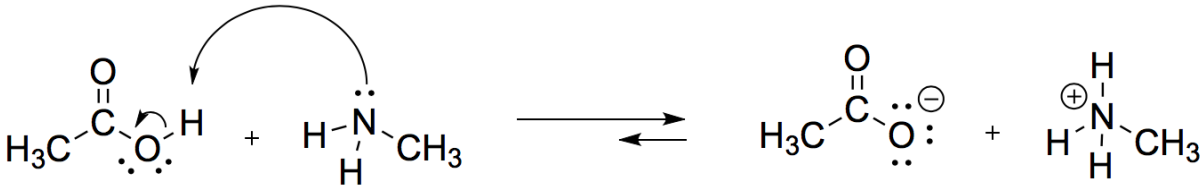


Figure 12. Proton transfer from an acid to the base in the first step of acid-base catalysis.

Common ways to distinguish nucleophilic catalysis from base catalysis are *"Common ion effect"*, detection of a covalent intermediate, nonlinearity of the Brønsted plot and the solvent isotope effect. *"Common ion effect"* is measured by adding the anions in the reaction, which are identical to the leaving group. From the obtained reaction rate, it can be concluded that faster rate corresponds to the base catalysis and slower to the nucleophilic catalysis, which consequently leads the reaction back to the intermediate, because of the additional anions. Detection of a covalent intermediate gives a confirmation of the nucleophilic catalysis by the intermediate isolation, spectroscopic detection or by the intermediate modification with the *"trapping agent"*.

3.2 Methods of carbamate synthesis

3.2.1 Direct *(in situ)* method *via* phosgene

Direct synthesis of the carbamates follow the reaction between phosgene, amine and alcohol in one step, where carbamates are directly obtained at the end of the reaction. Since possible formation of hydrogen chloride, which shows problematic effects on the environment, direct method might be used as an alternative procedure.[1] On the other hand, various replacements of phosgene substituents were recently introduced in the direct method, due to its poisonous properties. Some of them are 1,1,1-trichloromethylformate (diphosgene) and bis-(1,1,1-trichloromethyl) carbonate (triphosgene).[2] Contrary to the gaseous phosgene, diphosgene is a liquid at the room temperature, which makes reaction set-ups safer. Unfortunately, diphosgene is not stable and decomposes further to the phosgene and chloroform. Triphosgene is a solid and considered as a safe alternative of phosgene. It provides better solubility and lower toxicity.[55] Consequently, it has various applications, including synthesis of ureas.

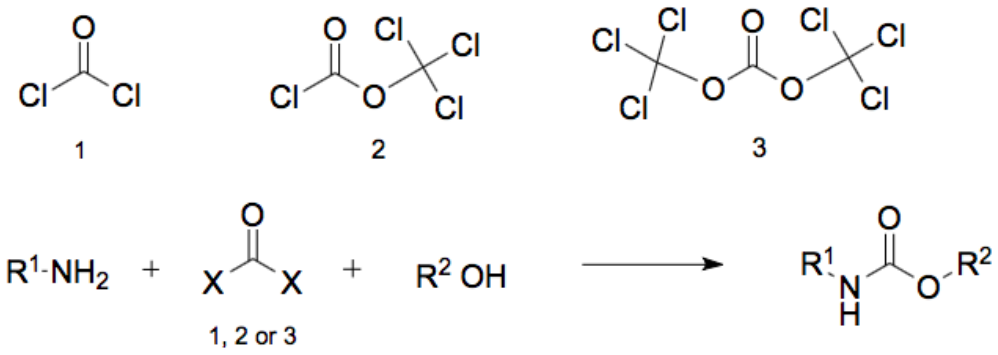


Figure 13. Scheme of in situ reaction of phosgene (1) and its derivatives; diphosgene (2) and triphosgene (3).

Chloroformates and isocyanates appear as intermediates, depending on the reaction pathway. Therefore, chlorocarbonyl derivatives are obtained, when phosgene first reacts with the aliphatic or aromatic alcohols and reacting further with amines, i.e. aminolysis, to form carbamates. If the phosgene reacts with phenol and primary amine, aryl carbamates might be produced. The synthesis requires strong basic conditions, using NaOH, $NaHCO_3$, Et_3N, etc.[2] On the contrary, parallel reaction of the phosgene with the amines gives carbamoyl chlorides or isocyanates, which generate carbamates after the reaction with alcohol. It has been shown that reaction between phosgene and primary or secondary amines gives symmetrical urea derivatives with the high yields.[55]

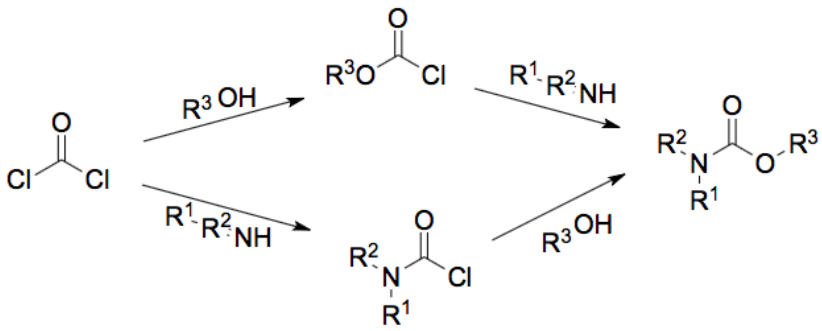


Figure 14. Generation of carbamates from phosgene through chloroformates and isocyanates.

Mormeneo and his co-workers have reported a new *in situ* method of carbamate formation, replacing phosgene with triphosgene (Bis-(1,1,1- trichloromethyl) carbonate; BTC). This one-pot reaction provides high yields from various alcohols and amines.

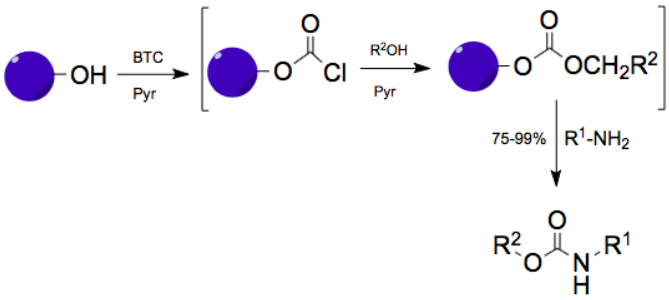


Figure 15. Scheme of Mormeneo in situ method.

Isocyanates, however, are obtained from the initial reaction of phosgene and amines, which further reacts with the aliphatic alcohols or phenols. This method is the most common way to produce carbamates. Moreover, this procedure also allows carbamates to polymerize into polyurethanes under the basic reaction conditions.[2]

1. Carbamate synthesis with amines

Reaction of aromatic amines with organic carbonates

Carbonates can be formed directly from the reaction between phosgene and alcohol. Therefore, the reactions starting with the carbonates might be considered as the method *via* phosgene route. Alternative synthesis between organic carbonates and aliphatic amines, proceeds smoothly without an additional catalyst. Reactions with weak bases like aromatic amines, on the other hand, are theoretically possible without the catalyst, but take too long to be used as actual preparative method. To obtain reasonable yields in shorter time, catalyst must be applied. Therefore, strong bases, such as metal alkoxides or compounds zinc, cobalt, tin, aluminium or titanium have been applied, showing successful conversion into carbamates (Table 1). Moreover, Lewis acids and metal alkoxides have been explored for the reactions of amines with dialkyl and diarly carbonates.

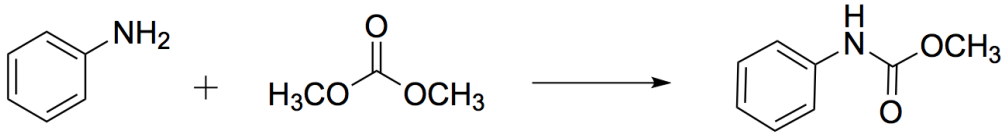
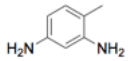
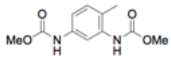
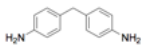
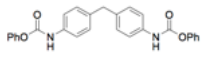


Figure 16. Carbamate formation from aromatic amine and organic carbonate.

Table 1. Reaction conditions between aromatic amines and organic carbonates.[56]

Amine	Carbonate[a]	Reaction conditions; Molar ratio of amine/ carbonate /catalyst	Carbamate	Yield (%)
$PhNH_2$	DEC	Al, I_2, $HgCl_2$, 130 °C, 18 h; 1:10:0.23 [Al]	$PhNHCO_2Et$	92[c]
	DMC	Lead octanoate, MTO[b], 180 °C, autoclave 2h; 1:28:0.008		92[c]
$PhNH_2$	DMC	$Zn_4O(O_2CNEt_2)_6$, 170 °C, 6080 Torr, 2h; 1:5:0.01	$PhNHCO_2Me$	97[d]
$PhNH_2$	DEC	$Ti(OBu)_4$, 130-140 °C, 6-7 h; 1:3:0.01	$PhNHCO_2Et$	96[d]
$PhNH_2$	DMC	$Zn(OAc)_2$, 140 °C, 6840 Torr, 6 h; 1:5.2:0.09	$PhNHCO_2Me$	99.8
	DPC	$Ph_2P(O)OH$, 90 °C, 7 h; 1:1.9:0.01		91[d]

[a] DBC: dibutyl carbonate;DEC: diethyl carbonate;DMC: dimethyl carbonate;DPC: diphenyl carbonate.
[b] MTO: mineral turpentine oil.
[c] HPLC yield.
[d] Isolated yield.

Reaction of aromatic amines with inorganic carbonates

Carbamates can be achieved from inorganic carbonates, e.g. potassium carbonate, used as a carboxylating agent and alkyl halides as the alkyl source. The reaction must include heterogeneous solid-liquid technique, using tetraethylammonium hydrogen sulfate as a phase-transfer catalyst. For achieving good yields, the reaction requires an aprotic solvent with an excessive amount of added catalyst.

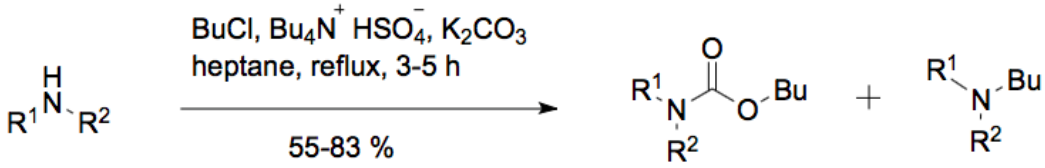


Figure 17. Carbamate formation from the reaction of amine with inorganic carbonates under phase-solid conditions.[57]

Enzyme-catalyzed reactions with organic carbonates

The chiral carbamates can be obtained from the enzyme-catalyzed reactions of amines and organic carbonates. Therefore, two reactions have been widely employed, i.e. esterification and transesterification. The reaction might follow either an enzymatic alkoxycarbonylation, using racemic amines as a starting material, or kinetic resolution of racemic vinyl carbonates. Consequently, *R*-enantiomers are resulted from racemic amines, when enzyme is taking after Kazlauskas rule.

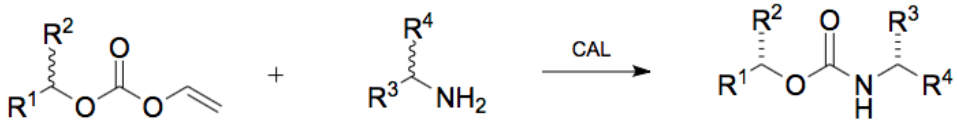


Figure 18. Enzyme-catalyzed carbamate formation form amines and vinyl carbonates.[58] CAL refers to catalytic enzyme Candida Antarctica lipase SP 435A.

Carbamate synthesis from cyclic organic carbonates

Carbamates might be synthesized from the reaction between cyclic carbonates and amines. It has been reviewed that unsymmetrical cyclic carbonates provide an isomeric mixture of two corresponding carbamates under the thermodinamic equilibrium.[59]

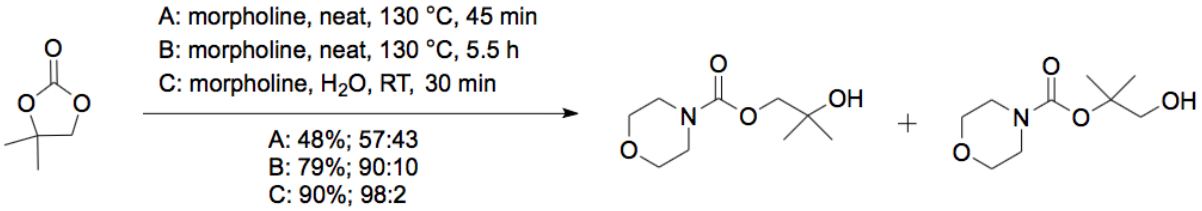


Figure 19. Isomeric carbamates formation from the amines and cyclic carbonate.[59]

Carbamate synthesis from primary or secondary amines and chloroformates

Chloroformates can be obtained as an intermediate in one of the phosgene routes of the carbamate synthesis. The drawback of this procedure is the presence of acyl halide, forming hydrogen chloride, which takes half of the amine in the reaction and consequently needs to be eliminated.[51] Since additional elimination causes instability of chloroformates, they should be freshly prepared through either phosgene route or with benzyl chloroformate (CbzCl).

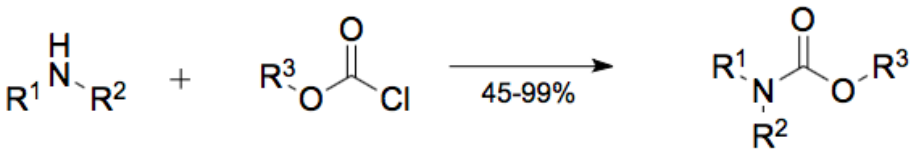


Figure 20. Reaction of secondary amine with chloroformate.[60]

2. Carbamate synthesis with urea

One of the extensively used processes of carbamate synthesis consists of the reaction between the alcohols and amines with ureas, which play a role as a carbonyl source. Usual laboratory preparation of ureas is followed by the reaction of phosgene with the primary or secondary amines through an isocyanate intermediate. Another possible procedure is the reaction between the phosgene and ammonia. However, ureas are economically affordable initial reagents, used for the *N*-unsubstituted carbamate synthesis. Under requisite high temperature, amine and alcohol attach one on each side of the urea, following the reaction with double nucleophilic addition and consequently obtaining carbamates in good yield. Therefore, two moles of ammonia result as a side product. It has been reported that removing either the ammonia or additional amine byproduct from the solution, improves reaction yield. The procedure can be proceeded either without or with a catalyst, therefore using Lewis acids, organic or inorganic bases, transition metal compounds, etc. [61]

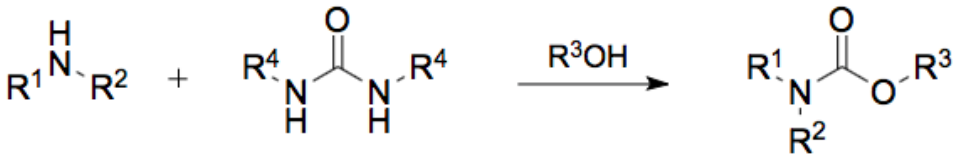


Figure 21. Reaction of ureas with amine and alcohol.[61]

Upon heating of urea and alcohols, urea decomposes into ammonia and isocyanate. As already discussed above, removing ammonia from the reaction improves the final yield. Isocyanate reacts further with an alcohol to form a carbamate. Commercial route for synthesizing methyl or ethyl carbamate follows the reaction pathway of urea with various alcohols, i.e. the urea method.[62]

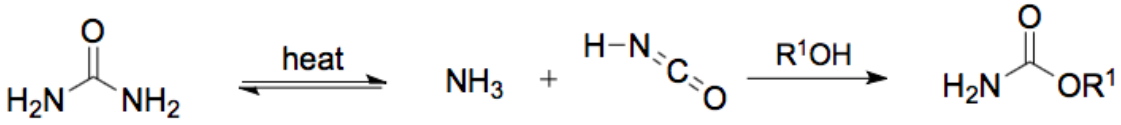


Figure 22. Reaction of high-boiling alcohols with urea.

Moreover, ureas also interact with carbon monoxide, organic carbonates or oxiranes. Reaction of ureas towards CO follows similar manners as with amines, obtaining good yields under the presence of a catalyst and an oxidizing agent. As shown in Figure 23, two different products might be obtained. To avoid the formation of the carbamate mixture, both substituents, i.e. R^1 and R^2, should be the same.

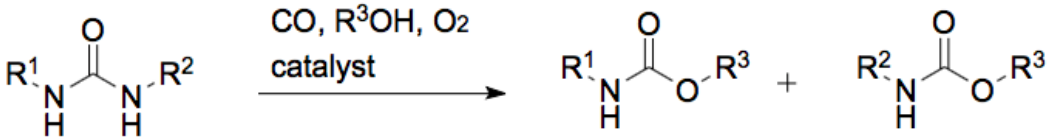


Figure 23. Synthesis of carbamate mixture of urea with alcohols, carbon monoxide and molecular oxygen.

Urea reaction, with the organic carbonates, is set up under the heating along with the catalyst and a co-catalyst, formed from iodine and mercury salt. Often used catalysts are base catalysts or either organic or inorganic compounds of lead, titanium, zinc, tin and aluminum, where the latter proves to be the most commercially available, due to its inexpensiveness. Additional advantage of this process is application to the formation of polyureas.[63]

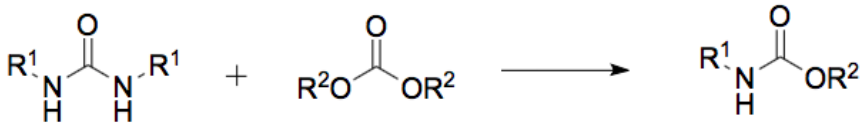


Figure 24. Carbamate formation from ureas with organic carbonates.[63]

The third method of carbamate synthesis from urea refers to a reaction with epoxides under the superatmospheric pressure. In the first step, the reaction is subjected to nucleophilic attach of the urea onto epoxide to form an intermediate. In the next step, intramolecular nucleophilic attack forms cyclic intermediate, which yields into the final carbamate product.[64]

Figure 25. Carbamate synthesis from urea and epoxide.

3.2.2 Indirect method *via* isocyanate

Indirect carbamate synthesis consists of two steps. Starting compounds in the first reaction are phosgene and amine, primarily forming chloroformamides. Upon heating, they eliminate hydrochloric acid to produce isocyanate as an intermediate.[65] Additional hydroxyl compounds, i.e. alcohol or phenols[66] are added into the reaction system to form carbamate, using strong bases[67] or metal halides[68]. However, the usual procedure of carbamate formation is through the reaction between isocyanate and alcohols, involving inorganic cyanates and alkyl halides to obtain alkyl isocyanates.[1] Carbamates can be also achieved by using an ultrasound.[69] Based on the acid-base equilibrium reaction in the second step, carbamates can be converted backwards into isocyanates, using higher temperature and different catalysts, such as metals (Figure 26).[70]

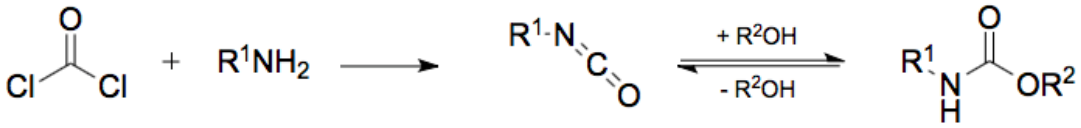


Figure 26. Indirect synthesis of carbamates via isocyanate route.

Another way of formatting carbamates may be from Curtius, Hofmann or Lossen rearrangements, where isocyanate appears as an intermediate, normally in the synthesis of primary amines through hydrolysis.

1. Carbamate synthesis with isocyanate

Carbamate cyclization from isocyanates with alcohol

Reaction of isocyanates with alcohols is known as an alternative method for carbamate synthesis, where standard procedure follows the reaction pathway between active hydrogen and isocyanate nitrogen. It has been reported that primary amines react easily, while the reaction with secondary and tertiary amines usually requires the additional catalyst, e.g. pyridine or sodium methoxide. Moreover, the carbamate cyclization with the terminal alkynyl alcohols might be carried out under the elevated temperature. Figure 27 is showing *in situ* reaction of propargyl alcohols and isocyanates under the catalytic amount of sodium methoxide, producing cyclic carbamate with good yield (70%).[71]

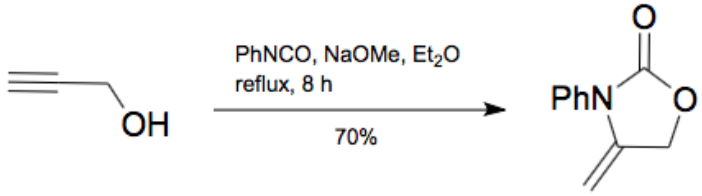


Figure 27. Catalyzed-reaction of terminal alkynyl alcohols with isocyanates.[71]

Synthesis of cyclic carbamates from cyclic carbonates with isocyanates

An alternative method of carbamate cyclization with the isocyanates involves cyclic carbonates as a starting material, which might also provide backbone of the carbon atom. Frequently used catalysts in the reaction are either inorganic salts or tertiary amines.[72]

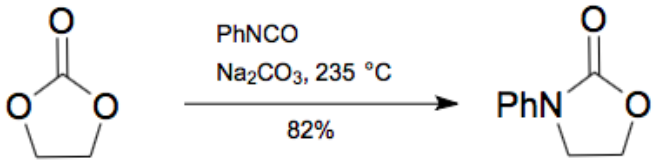


Figure 28. Reaction of phenyl isocyanate with cyclic carbonate.[72]

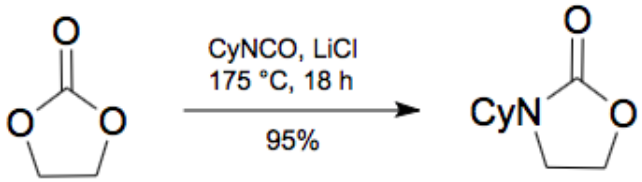


Figure 29. Reaction of cyclohexyl isocyanate with cyclic carbonate.[72]

Two mechanisms are possible, depending on the thermal conditions of the reaction. If the temperature not higher than ambient temperature, the complex of the isocyanate and carbonate is formed as an intermediate. Upon heating, the molecular complex degrades to oxazolidin-2-one (Figure 30) by CO_2 elimination of the carbonate (approx. 90%) and isocyanate (10%).[73]

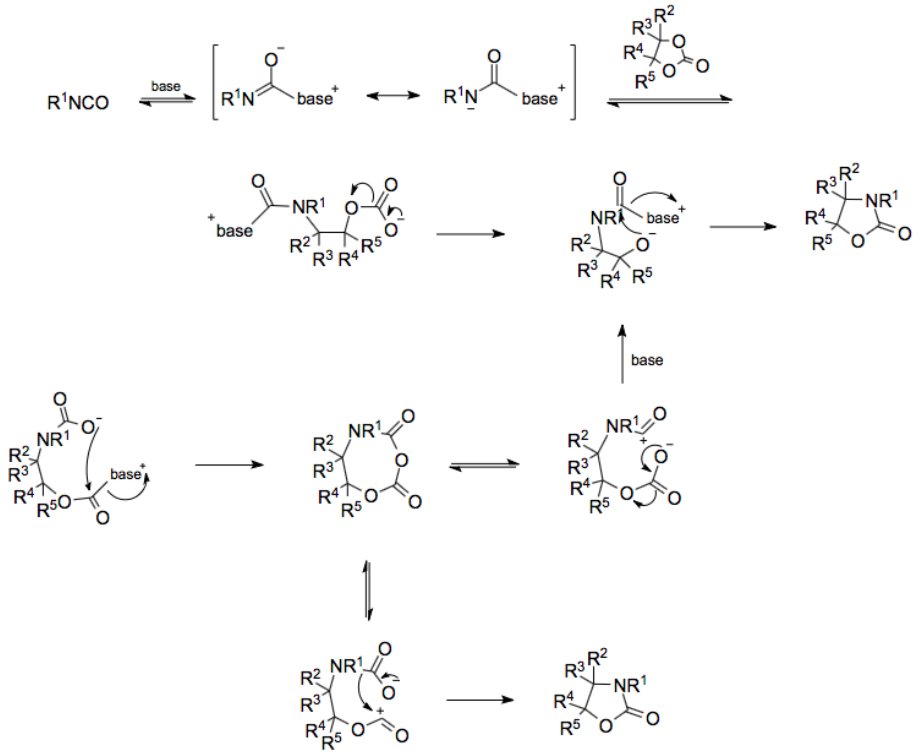


Figure 30. Mechanism of cyclic carbamates synthesis from isocyanate and cyclic carbonate under basic catalytic conditions.

Synthesis of carbamates with amines

One route of carbamate synthesis might be proceeded from amines and dimethyl carbonate (DMC), which is applied as a replacement of phosgene. However, the synthesis of DMC still requires methanol as a starting material under highly consumed procedure. To conclude, this process might not be entirely toxic-free and convenient, but is still considered as a friendlier method than phosgene route.[74]

2. Synthesis of *N*-aryl carbamates

Standard procedure for the synthesis of *N*-aryl carbamates is the reaction from an alcohol and isocyanate.[75] A lot of attention has been recently given to their formation from polyfluorinated alcohols, due to the various features of the fluorinated organic compounds, such as chemical stability, hydrophobicity and low surface energy[76], which make them applicable in pharmacy, catalysis and material science.[77] However, polyfluorinated alcohols are weak nucleophiles, which consequently result in having no interactions with alkyl isocyanates and weak interactions with aromatic isocyanates at the ambient temperature. Furthermore, the alternative reactions with amines[77] or highly electronegative carbamates in Hofmann rearrangement[78], require the additional catalysts. Hence, polyfluorocarbamates derivatives have not been applied in many fields.

Recently, a new radical mechanism of the reaction between polyfluorinated and phenyl isocyanate have been introduced.[79] The reaction procedure has been carried out in the mild specific conditions, reporting that polyfluoro alcohols have higher acidity than usual alcohols, e.g. ethanol pK_a = 29.8; TFE pK_a = 23.5. This feature provides higher reactivity and opportunity of mechanistic studies for polyfluoroalkoxy radicals.

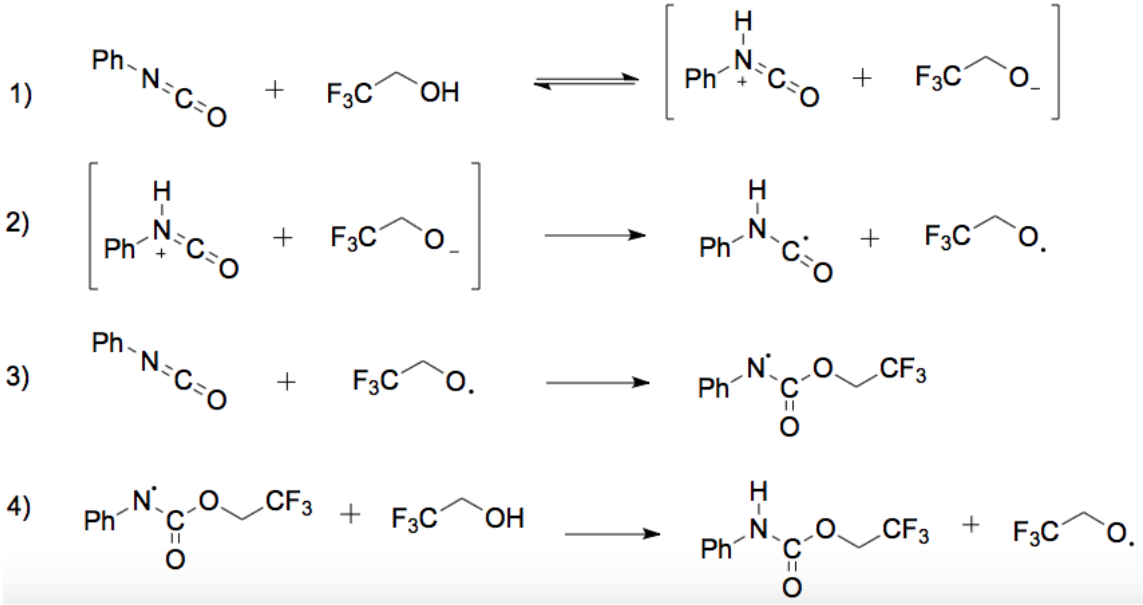
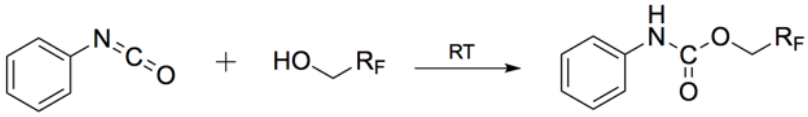


Figure 31. Radical chain mechanism of phenyl isocyanate and trifluoroethanol under initiation (1,2) and propagation (3, 4) process.[79]

Aryl carbamate derivatives can be also obtained from the photochemical reactions between aromatic isocyanates and polyfluoro alcohols (or diols). This apporach has been also confirmed as a less toxic procedure for the environment[80]. Providing the photochemical activation either extensively improves or enables the formation of polyfluorocarbamates in different solvents. Therefore, Tables 2 and 3 are showing the results, obtained at the room temperature and under photochemical conditions in two different solvents (ACN and DCM), showing enormous improvement of the product yields in ACN. Moreover, the reaction with the initial reagent, TFE, is providing the best results.

Table 2. The reaction between phenyl isocyanate and TFE at the room temperature. Reaction conditions: 0.5 mmol of PhNCO, 1.0 mmol of fluorinated alcohol, dry ACN, under nitrogen, 60 min irradiation with mercury high pressure lamp Philips HPK 125W.[81]



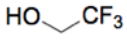
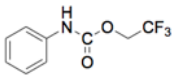
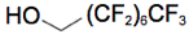
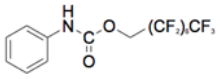
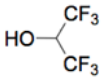
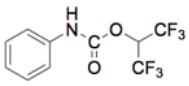
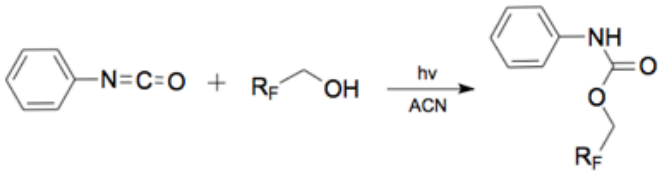
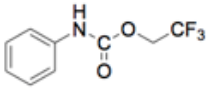
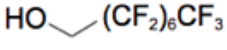
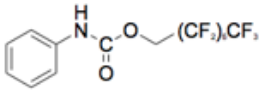
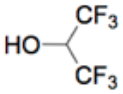
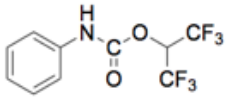
Entry	Alcohol	Product	Solvent	Yield (%)
1			ACN	0
2			DMF	93
3			ACN	0
4			DMF	58
5			ACN	0
6			DMF	80

Table 3. The photochemical reaction between phenyl isocyanate and TFE. Reaction conditions: 0.5 mmol of PhNCO, 1.0 mmol of fluorinated alcohol, dry ACN, under nitrogen, 60 min irradiation with mercury high pressure lamp Philips HPK 125W.[81]



Entry	Alcohol	Product	Yield (%)
1			87
2			36
3			66

3. Curtius rearrangement

This method is a thermal degradation of an acyl azide to an isocyanate, established by Theodor Curtius in 1885.[82] The reaction might be catalyzed by Brønsted or Lewis acids with the acyl oxygen coordination.[83] Since there is no attached hydrogen on the azide, isocyanate formation occurs by the electron pair donation of a nitrogen atom to the carbonyl through the nitrene intermediate (Figure 33). The latter has an atypical configuration with the filled sp_2 orbital and completely empty p orbital. Consequently, nitrogen atom becomes highly electronegative, which generates rearrangement with the carbon atom in the molecule, giving new carbon - nitrogen bond. Isocyanate reacts further with either nucleophilic water, which produces primary amines by spontaneous decompose from losing CO_2 molecule, or alcohols; producing carbamates or amines; producing urea derivatives.[84] Moreover, photochemical pathway is possible, producing nitrene intermediate with the loss of a nitrogen gas.

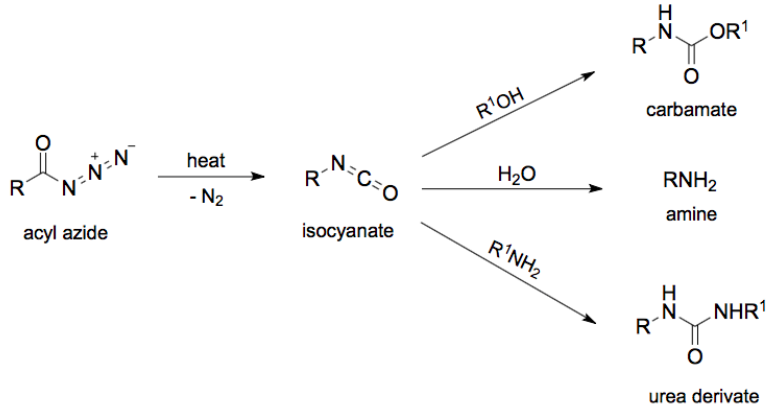


Figure 32. Scheme of Curtius rearrangement.

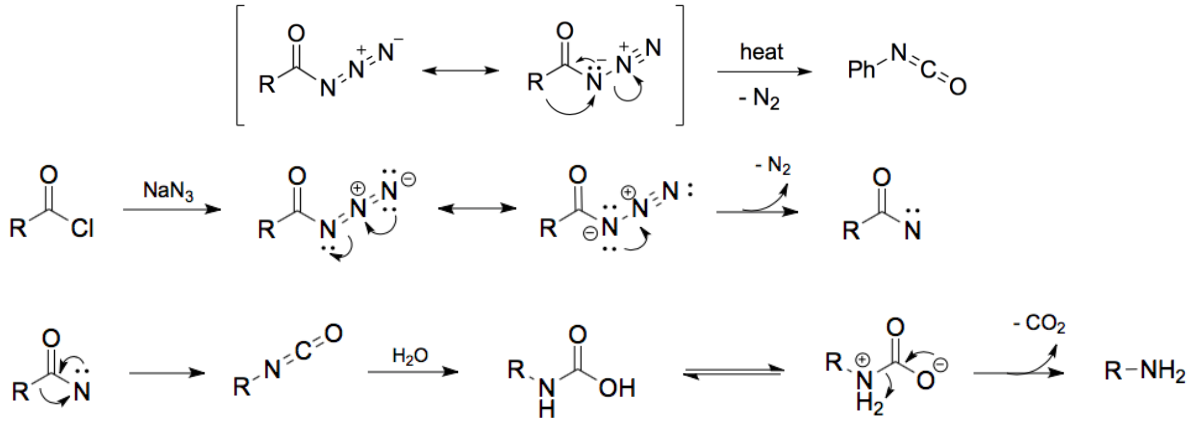


Figure 33. The mechanism of Curtius rearrangement.

4. Hofmann rearrangement

Hofmann rearrangement, developed by August Wilhelm von Hofmann, is an organic reaction used for converting primary amide to a primary amine. Therefore, the reaction can be performed directly in the aqueous solution, unlike in Curtius rearrangement. Reaction starts with the amide deprotonation using strong base, followed by the halogen attack to yield *N*-haloamide. The second deprotonation forms isocyanate as an intermediate, which further reacts with water, giving primary amine by decarboxylation of carbon dioxide (Figure 35).[85] In the isocyanate molecule, carbon is strongly attached to the nitrogen and oxygen, highly electronegative atoms, which produce a great electrophilic carbon. Further reaction with the alcohol provides formation of carbamate.

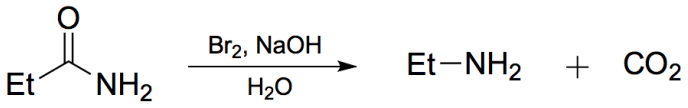


Figure 34. Scheme of Hofmann rearrangement.

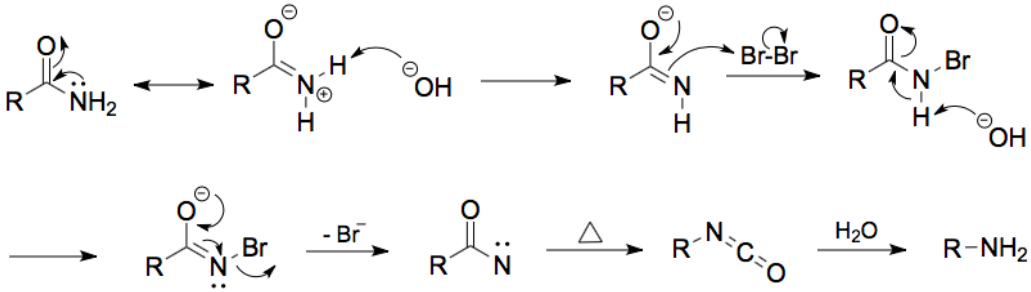


Figure 35. The mechanism of Hofmann rearrangement.

5. Lossen rearrangement

Lossen rearrangement is a convenient reaction of an isocyanate formation from a hydroxamic acid, named after Wilhelm Lossen. Comparing with Curtius and Hofmann rearrangements, Lossen allows to produce isocyanate under milder reaction conditions, such as lower temperature. The isocyanate is formed using base and tosyl chloride (Figure 36). Formation of carbamates can be achieved by trapping isocyanate intermediate with an alcohol, using many different nucleophilic catalysts (Figure 37).[86] Various alcohols can be applied under optimized conditions, especially primary and secondary, to reach high yield. However, tertiary alcohols provide carbamates in low yield due to steric hindrance.

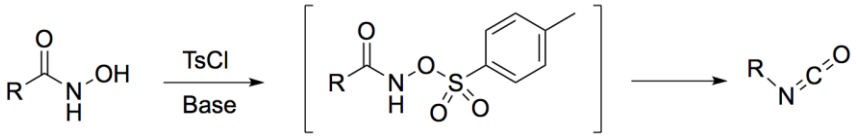


Figure 36. Scheme of Lossen rearrangement via hydroxamic acid O-derivative.

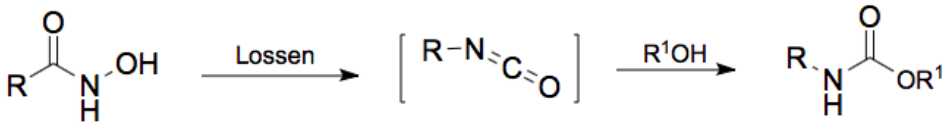


Figure 37. Scheme of Lossen rearrangement with further formation of carbamate.

3.2.3 Reactions with carbon dioxide

1. Carbon dioxide

Carbon dioxide is a colorless gas, present in Earth's atmosphere and naturally produced from volcanoes, hot springs and geysers.[26] Commercially, it has various applications such as fire extinguishers, air conditioning, solvents for the reactions in cleaning fluid, water treatment, food and agro-chemicals, etc. Partially it is also obtained as a product from coke combustion.

$$C(coke) + O_2(g) \longrightarrow CO_2(g)$$

Figure 38. Formed CO_2 from the coke combustion.

Anthropogenic emissions of CO_2 have been primarily increased from the carbon-containing fossil fuels, causing global warming.[87] Consequently, using an excess of produced CO_2, has become one of the major topics related to environmental issues. It is as well examined as a renewable source, however, hard to activate due to its strong stability. Therefore, carbonyl carbon electrophilicity and catalytic nucleophilicity should be increased.[88]

The employment of carbon dioxide for the synthesis of urea and salicylic acid in the synthetic chemistry, has been an operation in the industry since 1950's, similarly for the syntheses of inorganic carbamates.[89] One of the CO_2 applications for material synthesis with higher efficiency is the catalytic reaction from epoxides, resulting polycarbonates and cyclic carbonates (Figure 39). This reaction has been recently studied as a potentially successful reaction pathway for decreasing CO_2 level in the atmosphere.[90]

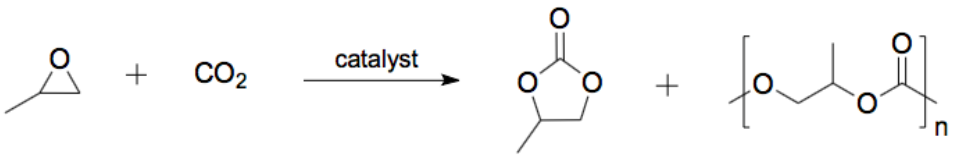


Figure 39. Formation of poly (propylene carbonate) and propylene carbonate from coupling reaction between CO_2 and epoxide.

2. Carbamate synthesis with carbon dioxide

Many methodologies have been established for recycling in converting atmospheric CO_2 into useful compounds. Since the alternative reaction contains very toxic phosgene and isocyanate, carbon dioxide indicates promising replacement as a more environmentally friendly compound, due to its nontoxic, noncorrosive and nonflammable properties. Organometallic reactions were proved to be a successful substitute of phosgene, where metal centers can work as one of the CO_2 catalysts. Best working transition-metal catalysts for primary amines are with Ni, Co, Mn, Ru and Pd. Among them palladium(II) salts or complexes are known to be a promising catalyst for carbamate formation with aliphatic and aromatic amines.[91] As mentioned previously, one of the important features are synthesis of polyurethanes, where carbamates are the crucial precursors. The reaction follows non-isocyanate pathway under S_N2-type mechanism with the alcohol.[20] Carbon dioxide itself is weakly reactive with nucleophiles, however, in the reaction with amines forms unstable carbamic acid, which further undergoes electrophilic conditions with alkyl halides in the presence of a strong Lewis base e.g., 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[92], to form a carbamate.[93] Main waste products of the reaction are acid halides, which can be problematic for the environment. Other source of carbamate syntheses from carbon dioxide can be metal alkoxides and alcohols, where the latter are proved to be less toxic for the habitat.[93]

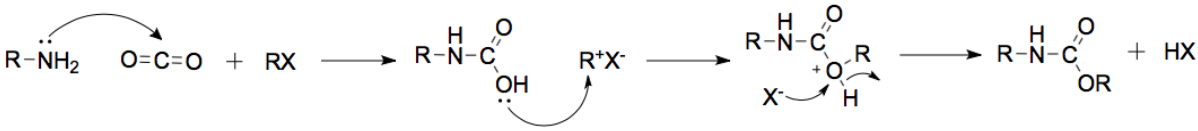


Figure 40. Reaction mechanism of carbamate synthesis of carbon dioxide, amine and catalyst.

Sakakura and co-worker[94], introduced another pathway with carbon dioxide, amines and alcohols, where carbonate is the first synthesized from an alcohol and CO_2 and catalyzed by inorganic complexes (Figure 41). Low conversion of the alcohol was explained as consequence of produced water, which was removed afterwards by a dehydrating agent. This reaction was shown as entirely phosgene- and halogen-free.

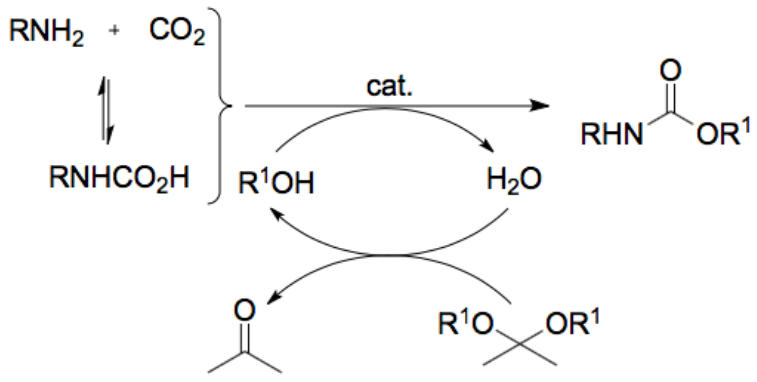


Figure 41. The carbamate synthesis via halogen-free route.[20]

Additional strategies for the CO_2 preparation of cyclic carbamates have been studied, since carbamate synthesis from CO_2 have been presented as more convenient than conventional methods with several drawbacks, such as toxicity or lack of stereoselectivity.[95] Some of the reported methods consist of CO_2 cycloaddition to epoxides, aziridines or amino epoxides[96]. Moreover, *in situ* performed transesterification between amines and cyclic carbonates has been shown as another strategy of carbon dioxide and epoxides cycloaddition.[97,98] The latest studies have been focusing on the addition of carbon dioxide to the acyclic unsaturated compounds like alkanes, alkynes and propagylic amines or alcohols[99], where amino alcohols (AAs) show an excellent supplier of the nitrogen atom due to their non-toxicity and inexpensiveness. However, they usually require high pressure and temperature with utilized catalysts, dehydrating agents or employed electrochemical conditions[96], which consequently provides cyclic urea as an outcome from the additional side reactions.[100]

Base-catalyzed reaction with carbon dioxide and amines

Carbamate synthesis under mild conditions require the use of strong bases. Their initial purpose is to drive the reaction towards carbamate formation. Moreover, they should make an oxygen of the carbamate anion more nucleophilic, by forming more achievable anion for the nucleophilic attack on an electrophilic substrate. Tertiary amines, on the other hand, provide low yields of carbamate formation, since they undergo different reaction mechanism than primary and secondary amines. However, the carbamate conversion can be increased by using strong amidine base, such as DBU. Stronger bases, such as pentaalkylguanidine (e.g. CyTMG), are giving even better yields, by creating larger charge delocalization, responsible for higher selectivity of the carbamate products. Moreover, increased ionic separation in solution makes the oxygen center more responsive and consequently improve the carbamate salt solubility in aprotic solvents.[101]

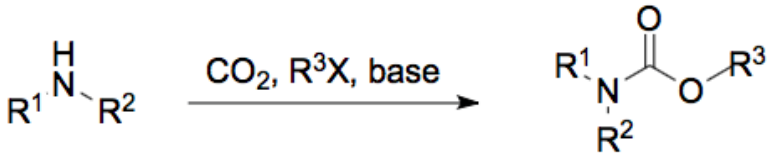


Figure 42. Base-catalyzed reaction of amines with carbon dioxide.[101]

Additional reaction with allylic compounds on a transition metal center has been reported. Strongly base-catalyzed reaction of carbamates with *O*-allylic groups can be carried out by allyl halide catalytic complex of palladium-tertiary phosphine catalyst (Figure 43). The reaction under nucleophilic conditions favors again the use of strong nitrogenous bases, e.g. DBU.[102]

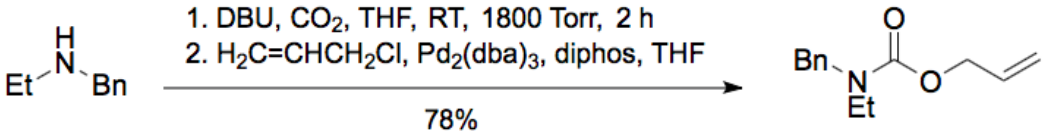


Figure 43. Base-catalyzed reaction of allyl carbamate synthesis with allylpalladium catalyst.[102]

Base-catalyzed reaction with carbon dioxide on a solid phase

Organic reactions, set on a solid phase, are very important, especially in the medicinal chemistry. Carbamate synthesis from carbon dioxide under this method can consists of Merrifield's resins, used as an electrophile and carbon dioxide as a carboxylic reagent (Figure 44). The good yield is obtained from an easy process of coupling the amines to the resin *via* CO_2 bridge.

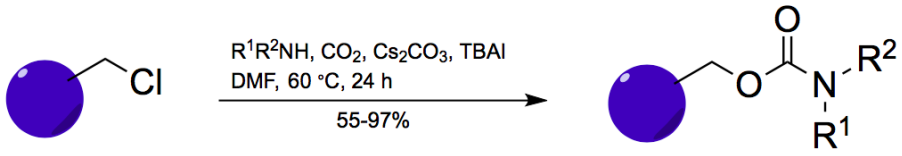


Figure 44. Solid-phase synthesis of carbamate using Merrifield's resins.[1]

Metal-catalyzed reaction with carbon dioxide

Metal-catalyzed reaction with carbon dioxide is giving the possibility to form carbamate from aliphatic and aromatic amines. The reaction might be catalyzed by several metal complexes, such as copper(I) *tert*-butoxide or zinc arylamide. Therefore, copper(I) carbamate can be obtained as an intermediate through the reaction between primary or secondary amines and carbon dioxide, which reacts further with the isocyanate, producing methyl carbamate (Figure 45). However, the obtained yields quite differ between each other.[1]

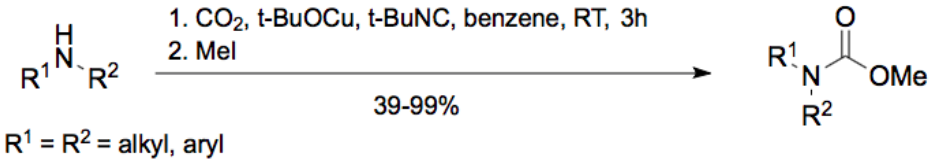


Figure 45. Carbamate formation from amine and CO_2 with copper(I) tert-butoxide.[1]

When the reaction is catalyzed by zinc arylamides, the reaction is set under high pressure and temperature, providing good yields of zinc carbamates (Figure 46). They have been shown as convenient intermediates in the arylcarbamates synthesis.

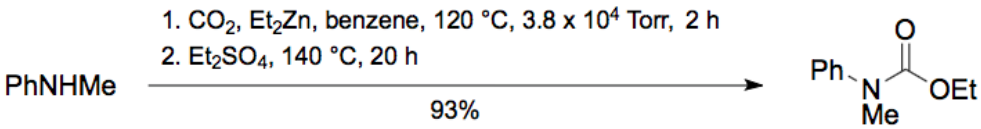


Figure 46. Zinc-catalyzed reaction of arylcarbamate formation from CO_2 and aromatic amines.

Over 90% of products in polyurethane industry contain aryl groups. Therefore, two possible arylcarbamate synthesis with CO_2 have been introduced, using either organic halides or tin alkoxides. Due to the lack of activity and toxicity of tin alkoxides, more desirable replacement with metal alkoxides has been employed, e.g. titanium alkoxide (Figure 47). The latter shows variety of useful features, such as being widely used, non-expensive and nontoxic.[74]

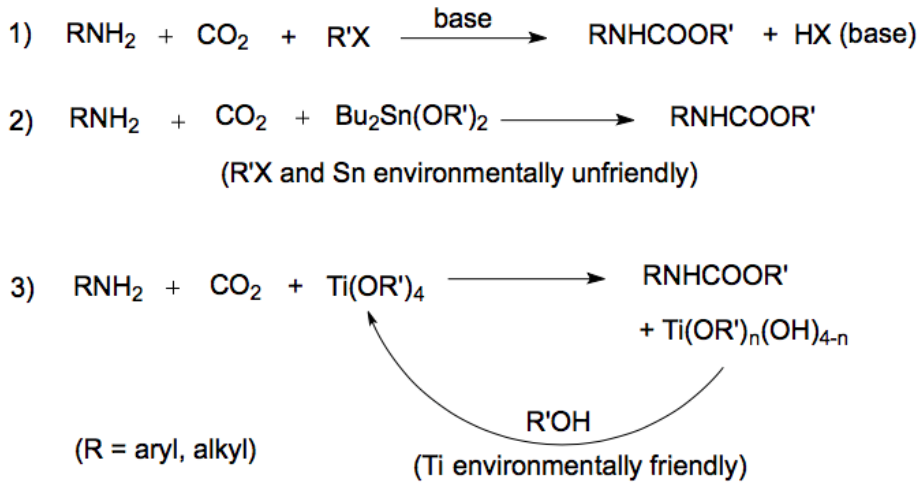


Figure 47. Synthesis of carbamates with CO_2.[74]

Figure 48 is representing the 3-step mechanism of carbamate synthesis with the titanium alkoxide, where titanium n-butoxide can be simply regenerated from butanol, keeping the same activity. The only obtained byproduct is water, which makes the entire process halogen-free. Moreover, the reaction represents environmentally friendly and phosgene-free method.[74]

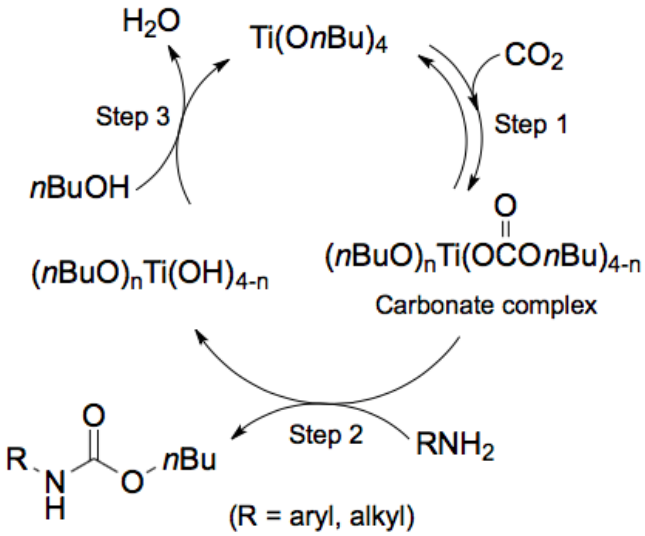


Figure 48. Possible reaction mechanism.[74]

Reaction of ammonium carbamates from carbon dioxide and amines

The synthesis of monoalkylammonium alkyl carbamates from the carbon dioxide has been shown to give good yields with primary amines. The usual procedure can be carried out in various solvents, such as non-polar solvents (benzene, toluene, diethyl ether) or polar aprotic solvents (DCM, ACN, tetrahydrofuran). Observed ionic carbamates have good stability in the saturated solution of the amines and CO_2. However, they degrade to starting reagents through carbamic acid, producing dimers or other complexes.

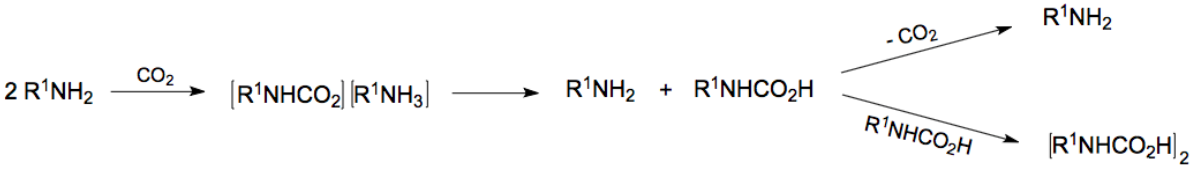


Figure 49. Synthesis of N-alkyl carbamate from amines and CO_2.

Despite unsuccessful reactions of alkyl halides with the primary amines, *N*-alkyl products might be obtained *via* electrophilic conditions. However, even when the reaction is carried out under elevated temperature and extremely high pressure, carbamate esters are formed in very low yield.[75] On the other hand, appearance of organic carbamates, e.g. macrocyclic polyether, provides preferable yield. Additional use of a crown ether increases solubility and improves the reactivity of carbamate anion nucleophile (Figure 50).

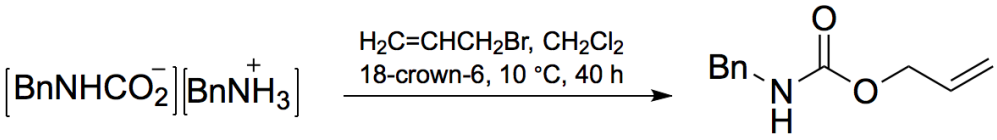


Figure 50. Synthesis of alkylammonium carbamates from primary amines and CO_2.[1]

Furthermore, compounds with double or triple bond may be applied, using transition metal complexes. Therefore, the reaction of ammonium carbamate to terminal alkynes steadily forms ethenyl carbamates in the presence of catalytic amounts with either dodecacarbonyltriruthenium(0) (*i.e.* $Ru_3(CO)_{12}$) or ruthenium(III) chloride (i.e. $RuCl_3$), yielding a mixture of *Z*- and *E*- isomers (Figure 51).[103]

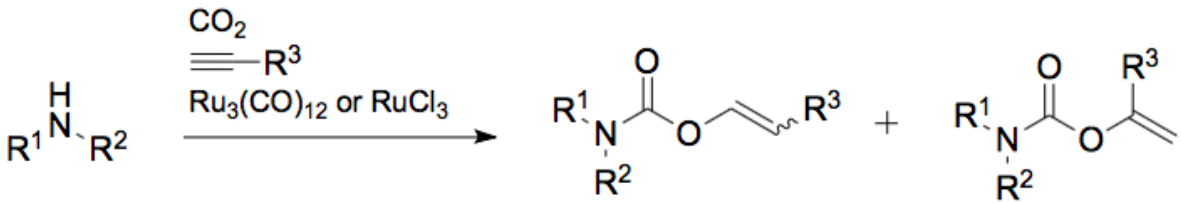


Figure 51. Ammonium carbamate reactions with terminal alkynes.[103]

3. Cycloaddition of carbon dioxide

Cyclic carbamates are formed in the nucleophilic reaction on the amine reactive site close to the nitrogen atom. Cycloaddition of carbon dioxide can follow four main procedures. Therefore, the reaction might follow the pathway into aziridines, epoxide-based synthesis, cyclization of unsaturated compounds and amino alcohol (AA) cyclization.

Cycloaddition of CO_2 into aziridines

The reaction between carbon dioxide and an aziridine follows [3+2] cycloaddition pathway under the presence of Lewis pair. Moreover, the reaction between 2-(aminomethyl)oxiranes and CO_2 can be performed in mild conditions, by stirring oxiranes methanol solution with CO_2 at the ambience temperature. Firstly, the nucleophilic amine group on the aziridine attacks carbon dioxide, which forms carbamate intermediate. The latter reacts spontaneously further into cyclic carbamate. In addition, the reaction might be described more in details, starting with the ring-opening nucleophilic attack, which is the driving force of the reaction, resulting from the ring strain in aziridines. In the next step, carbon dioxide takes place into the N-C bond of the aziridine ring, generating ring closure by the Lewis pair removal. Therefore, carbamate is formed (Figure 52). Several methods have been developed for oxazolidin-2-ones synthesis, such as aziridines carboxylation with CO_2, chloroformates, carbonates or other more complex procedures.[104]

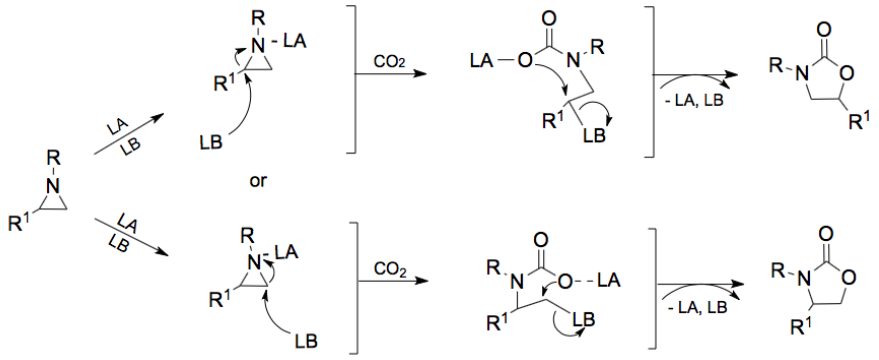
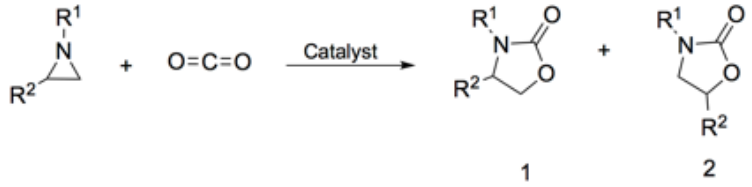


Figure 52. General reaction mechanism of [3+2] cycloaddition of carbon dioxide into aziridines, forming two possible regioisomeric products.

The reaction is frequently catalyzed, using either inorganic compounds[105], metal complexes[106] or organocatalysts[107]. However, the reaction might be performed also in the absence of the catalyst, such as *in situ* produced aziridinium carbamate salt, which relieves LA and LB.[108] Moreover, the reaction might be performed under supercritical conditions, obtaining cyclic carbamates with good yields and good selectivity. Regioselectivity is strongly determined by the used substrate and not by the catalyst. Since 5-aryloxazolidinones and 4-alkyloxazolidinones are produced (Table 4 below), it can be concluded that this method cannot be applied in pharmaceutical synthesis of antibiotics, as the 3-aryloxazolidinones and 5-alkyloxazolidinones are desired.

Table 4. The [3+2] Cycloaddition between 2-substituted aziridines and carbon dioxide with the substrate-controlled regioselectivity. [109,110]



R^1	R^2	Catalyst	Yield 1:2 (%)
H	Me	Zinc glutamate / Bu_4Br	94:0
H	Me	Iodine	72:0
H	Ph	Iodine	0:76
Pr	Ph	Functionalized titanium phosphonate	3:92
Pr	Ph	Zirconium phosphonate	5:70

Epoxide-based syntheses

Epoxide syntheses are based on the epoxide reaction with an amine and carbon dioxide. In the first step, epoxide reacts in parallel with the amine, forming amino alcohol (AA), while CO_2 and epoxide form cyclic carbonate, by the following [3+2] cycloaddition reaction. AA and cyclic carbonate react together to form cyclic carbamate. This method gives strongly regioselective 5-membered cyclic carbamate, which makes this method suitable for the synthesis of antibiotics. Neither catalyst nor substituent are determining the structure of the final product. Therefore, 5-substituted oxazolidinone consistently appears as the main product. Normally used Lewis pairs are potassium phoshate[111], ionic liquids[112] or metal complexes[113]. Another similar procedure is a reaction between CO_2 and epoxy amines, forming cyclic carbamates (Figure 53). The reaction might be performed under catalytic conditions or without a catalyst, under atmospheric CO_2.

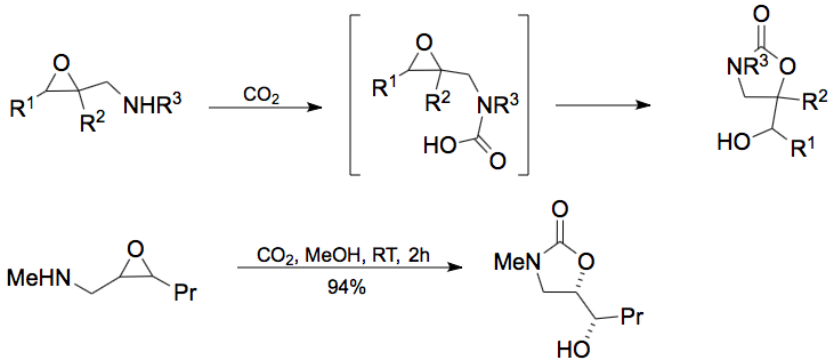


Figure 53. Reaction between an epoxy amine and carbon dioxide.

Cyclization of unsaturated compounds

Cyclization of unsaturated compounds might be performed with several different amines and alcohols, such as terminal alkynyl alcohols and amines, allylic and allenylic amines or alkenes and alkynes. The reaction conditions require elevated temperature and pressure with additional calatysts, such as copper salts or phosphines. However, no catalyst is needed when the reaction is performed under supercritical carbon dioxide.[114] The method provides good yields of *N*-substituted oxazolidin-2-ones from many different primary amines, without stereoselectivity.

Mechanism of the oxazolidin-2-one formation can be explained by primary formation of cyclic carbonate, which reacts further with an amine, breaking the C-O bond. Further cyclization continues with final step of dehydration. This procedure has been employed despite its effectiveness by only 2-methyl-but-3-yn-2-ol (Figure 54).

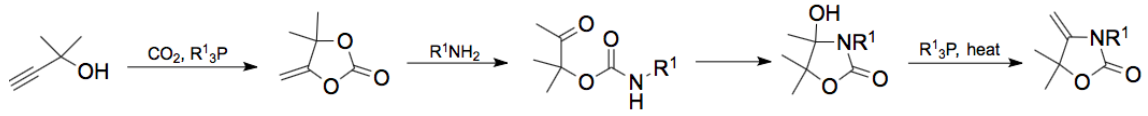


Figure 54. Mechanism of the reaction from terminal alkynyl alcohols with amines and carbon dioxide.[61]

Reactions from propargylic amines and carbon dioxide, on the other hand, are known to have two possible pathways. The Lewis base catalyst can first activate CO_2 or propargylic amine. Comparing to propargylic alcohols, tautomerization of oxazolones is almost never obtained in the reaction from propargylic amines.

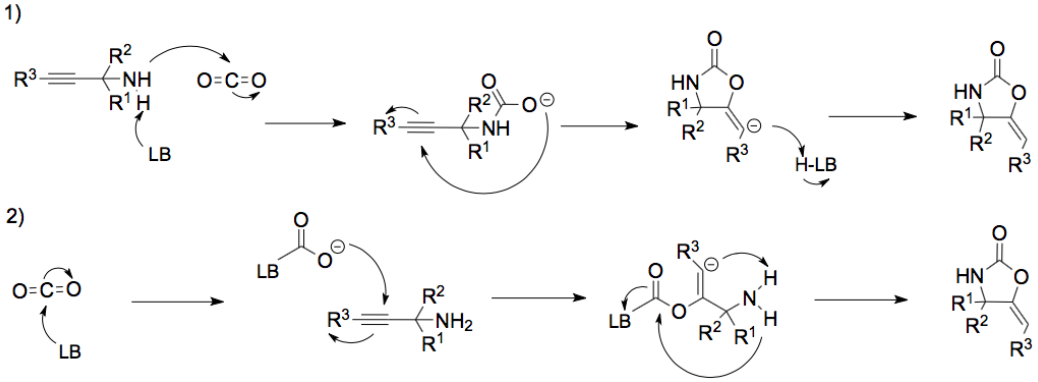


Figure 55. Two possible mechanism of the cyclization from propargylic amines and CO_2 under the presence of Lewis base; 1) Propargylic amine activated by catalyst and 2) CO_2 activated by catalyst.

The reaction of allylic amines with CO_2 yields into 5-substituted oxazolidiones. The reaction can be performed either *via* iodination[115] or fluoroalkyation[116] through double bond cyclization. As for the allenylic amines, the reaction is carried out similarly to propargylic amines, yielding selective 5-allyl substituted 2-oxazolidinones under catalytic conditions with either silver[117] or palladium[118].

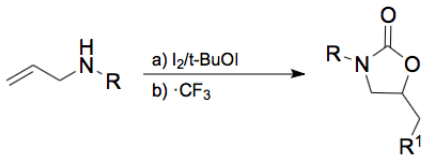


Figure 56. Carbamate cyclization from allylic amines and CO_2 either via iodination; R^1= -I (a) or fluoroalkylation; R^1= -CF_3 (b) of the double bond.

Cyclization of amino alcohols (AAs)

The reaction of amino alcohols cyclization requires quite inconvenient reaction conditions, such as high temperature and pressure with some additional side reactions.[119] Furthermore, it demands catalysts, supplemental reagent or electrochemistry. However, looking from the theoretical side, amino alcohols can be ideal reagents, by being inexpensive and available. Moreover, the only side product form the cyclization of AA with CO_2 is water (Figure 57).

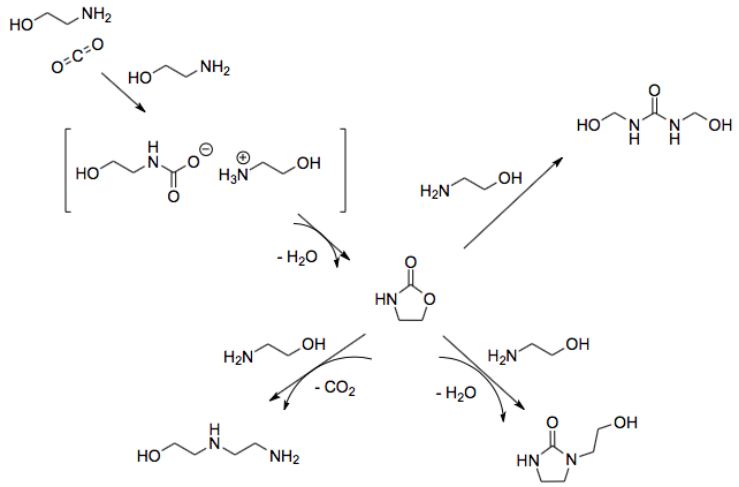


Figure 57. Formation of degredation products under high pressure and temperature without a catalyst in the reaction of AA and CO_2.

In the presence of catalysts, Lewis pair is used for the molecule activation. Therefore, LB activates the alcohol group, which attacks further the carbamate group, while LA is presence just occasionally as a cocatalyst. Possible catalysts contain seria, alumina, fluoride, etc.[120]

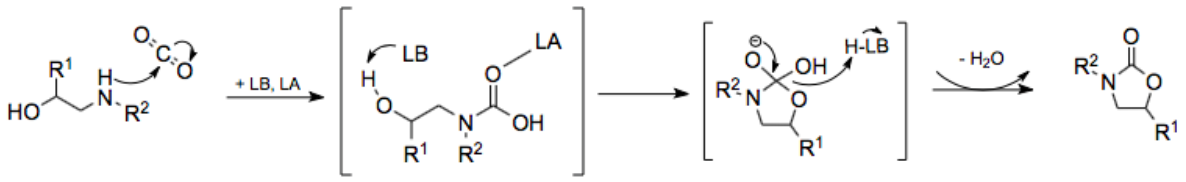
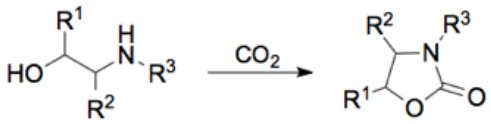


Figure 58. Reaction mechanism of AA and CO_2 with the presence of LA and LB.

To conclude, AA cyclization with CO_2 is providing a great variety of activation methods (Table 5) and synthesis of pharmaceutically useful carbamate rings.

Table 5. Various substituents and activation methods of the cyclization of AAs with CO_2.[121]



R^1	R^2	R^3	Activation method	Yield (%)
H	H	H	None (200 °C, 60 bar)	72
H	H	H	Catalyst (ceria)	99
H	H	Me	Sacrifical reagent (DCC)	69
Ph	H	H	Sacrificial reagent (Ph_3P)	88
Me	H	Ph	Sacrificial reagent (TsCl)	83
Ph	Ph	H	Electrochemical	87

3.3 Transesterification

In general, transesterification is a reaction of esters with alcohols, where the organic group, attached to an ester, exchanges with an alcohol organic group. The reaction is reversible and requires acid or base catalyst.[122] Therefore, the acid catalysts cause a proton donation, making carbonyl group more electrophile, while base catalysts eliminate the proton from the alcohol and make it more nucleophilic.

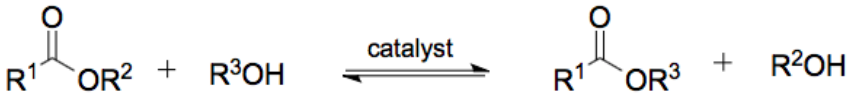


Figure 59. Transesterification of esters with alcohols under catalytic conditions.

Transesterification is a common method for the formation of complicated carbamates from the simpler ones. The reaction procedure contains alcohol heating under catalytic conditions, where one of the possible catalysts might be sodium alkoxide. Consequently, the reaction follows nucleophilic attack on the anion of carbonyl carbon from the carbamate. In general, acidic or base catalyst are used for the alcohols under low-boiling conditions.[123] In this work transesterification represents useful method of achieving the *N*-aryl carbamate product through phosgene-free route.

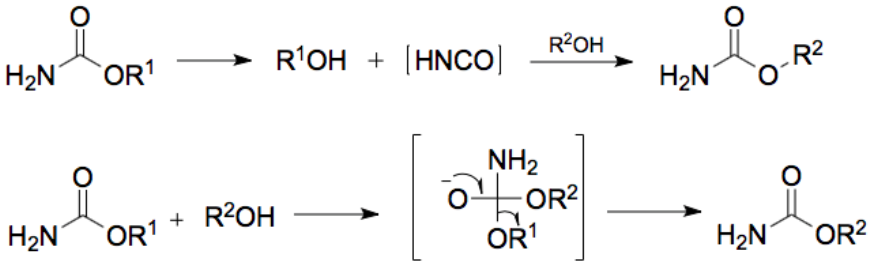


Figure 60. Reaction mechanism of carbamate synthesis with alcohol under acid or basic catalytic conditions.

When unsubstituted carbamate is employed as an initial reagent, the main mechanism is set on the reaction of displacement. However, decomposition might occur when using monosubstituted carbamates. Furthermore, the temperature must remain constant, otherwise carbamates of low-boiling alcohols can be formed from carbamates of high-boiling alcohols. Consequently, thermal dissociation of initial carbamates might result into isocyanate and an alcohol. Due to initial low boiling point of tertiary alcohols and phenols, they cannot undergo carbamate transesterification under acid or base catalysts.

The reaction mechanism in Figure 61 is presenting the chloride anion attachment on the alkyl group, achieving extended C-O bond and consequently obtaining better yield. On the contrary, attacking the phenol provides lower yield, due to the increased steric hindrance (Table 6).

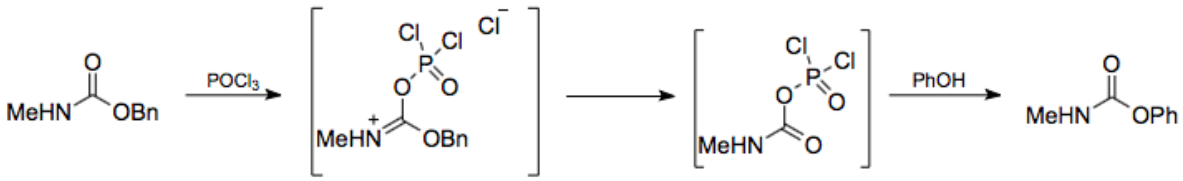
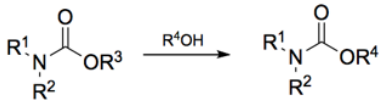


Figure 61. Transesterification of carbamates using phosphoryl chloride.[1]

Table 6. Methodologies of carbamate transesterification.[1]



R^1	R^2	R^3	R^4	Reaction conditions	Yield (%)
H	H	Et	Bn	Na, 160-170 °C, then 200 °C, 8 h	48
H	H	Et	$(CH_2)_2NEt_2$	reflux, 8 h	60
Bu	H	Et	$(CH_2)_2NEt_2$	toluene, $Al(OiPr)_3$, reflux, 12 h	80
Et	Ph	Et	iBu	iBuONa, reflux, 4 h	94
H	H	iPr	$(CH_2)_{17}Me$	$Ti(OiPr)_4$, 150-155 °C, 304 Torr, 75 min	99
Ph	H	Cy	Me	210 °C	90

Reaction of carbamates with amines or polyamines is one of the alternative methods for the conversion of *N*-unsubstituted to *N*-substituted carbamates without or with additional catalyst, i.e. pyridine, DBU and triethyamine.

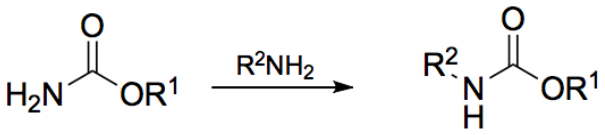


Figure 62. Carbamate transesterification with amines.[83-1]

Additional carbamates transesterification might be with alkenes, which depends on the regioselectivity of more substituted carbon of the double bond (Figure 63). The reaction is set under catalytic conditions, using either Lewis acids, sulfonic acid polymers, mineral acids or sodium borohydride.[124]

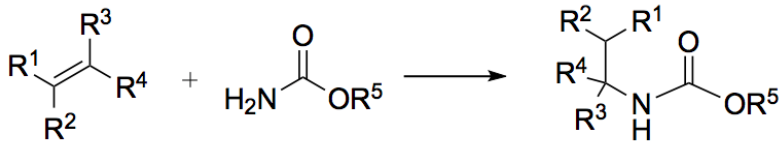


Figure 63. Carbamate transesterification with alkenes.[1]

4. Experimental

4.1 Introduction

The objective of this graduate work was to optimize the synthesis of *N*-aryl carbamate in the catalytic halide-free reaction. The method has been processed in two steps, starting with the initial reaction between bis(2,2,2-trifluoroethyl) carbonate (**3**) and aniline (Figure 65), forming carbamate intermediate (**4**) and continuing with the reaction of additional phenyl ethanol in the second step (Figure 66), forming final product (**5**). It has been reported that carbonate **3** represents a promising substitute, reacting smoothly with the alkyl amines, without any special conditions, while the reaction with aromatic amines, requires additional catalyst. Since there is no formation of a bond with a hydrogen, the first step of two-step reaction procedure undergoes nucleophilic catalytic reaction, where electronegative nitrogen of the aniline molecule attacks carbonyl carbon in the carbonate molecule **3**. Consequently, it eliminates one part of the carbonate, forming TFE as a side product and a carbamate as the main product, i.e. intermediate (**4**).

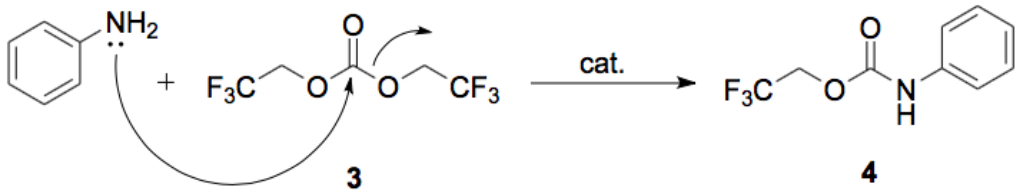


*Figure 64. The first step of the optimized catalytic reaction, forming carbamate intermediate (**4**).*

The second step consists of the reaction between **4** and additional phenyl ethanol. As the aniline part of the compound **4** possess a hydrogen atom, this step follows base catalysis, where Brønsted base is the main driving force of the reaction with the large proton transfer area in the transition state of the reaction. DBU has been shown as the most effective among all the catalysts used in the optimization process. Therefore, a proton is initially attacked by the base and followed by the TFE elimination. The obtained intermediate of the second step is phenyl isocyanate, which further reacts with phenyl ethanol. Consequently, the carbonyl carbon of isocyanate is attacked by the electronegative oxygen of an alcohol to form the final carbamate product (**5**), Figure 65.

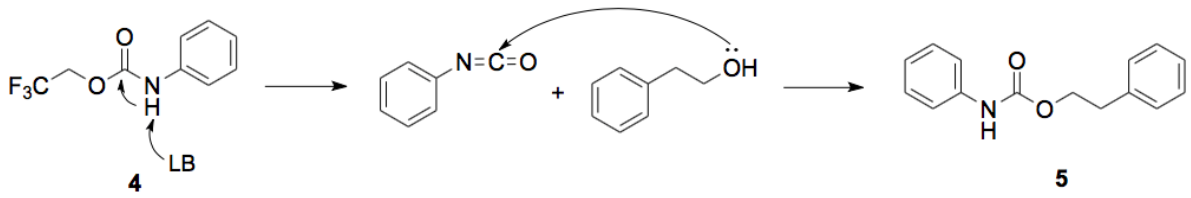


*Figure 65. The second step of the optimized catalytic reaction, forming carbamate product (**5**).*

This graduate work consists of two parts, the optimization process of two-step reaction and the formation of initial reagent **3** in the optimization process. Furthermore, two-step reaction is composed of optimizing the **4** formation in the first step and the final formation of **5** in the second step *via* isocyanate route. Final yields of compounds **4** and **5** were determined by calibration curve.

The second part showed an attempt of synthesizing the compound **3** from the propylene carbonate and TFE, catalyzed by the addition of five different metallic salts.

To conclude, the increased yields of **4** or **5** from the two-step reaction showed that higher temperature, increased amount of catalyst and time of the reaction are the most effective optimization parameters. Looking in the literature, formation of initial reagent **3** can be successfully formed from TFE and BTC, where the latter represents a beneficial replacement of the phosgene by making the reaction environmentally friendlier. Moreover, the by-product, i.e. trifluoroethylchloroformate, can be transformed back to **3** with the additional base, i.e. trimethylamine (Figure 66).[61] Yet, this procedure still represents undesirable process due to general formation of trifluoroethylchloroformate.

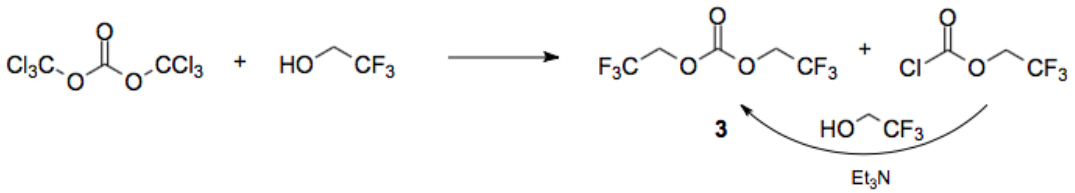


*Figure 66. Synthesis of bis(2,2,2-trifluoroethyl) carbonate (**3**).*

4.2 Experiments

The solvents and reagents were commercially supplied without further purification, unless otherwise specified, i.e. solvents were dried over activated 3 Å molecular sieves. Schlenk techniques were used when performing moisture and air-sensitive reactions under an inert atmosphere. Eluents, used for the flash chromatography, were tracked by silica gel on TLC Al foils and detected under UV light, using UV Mineralight lamp with multiband 254/366 nm. Column chromatography was on run with silica gel (40 – 63 μm). The IR spectrum was recorded on a Bruker ALPHA-P FT-IR spectrometer. GC-MS analyzes were performed on Agilent Technologies with 6890N Network GC System, 7683 Series Injector and 5973 Network Mass Selective Detector. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz at room temperature. Reported ^{1}H NMR data are provided in the following order: multiplicity (s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet), coupling constant and number of protons.

4.2.1 Two-step optimization process

The reaction followed two-step optimization process to obtain desired yields of the final carbamate product (**5**). The first two synthesis were performed between two different amines and carbonate **3**, where benzylamine represented alkyl amines and aniline represented aryl amines. It has been reported that compound **3** reacts smoothly with aliphatic amines without any specific conditions and gives a strongly regioselective product.[74] In this work it was discovered that aromatic amines are less reactive, due to delocalized electrons in the aromatic ring, hence, the additional catalyst must be applied. Since aniline was used in all further reactions, several different catalysts, i.e. DBU, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,1,3,3-tetramethylguanidine (TMG), 1,1,3,3-tetramethylthiourea (TMTU), were used to achieve good yields. Further syntheses also include other parameters, such as temperature, reaction time, increased amount of solvent, catalysts and different ratios between carbonate and phenyl ethanol, which were optimized to achieve satisfying yields of carbamate intermediate (**4**) and product (**5**). At the end, mesitylene was added in the solution as an internal standard for the evaluation of the GC-MS results. Yields were determined by calibration curve.

4.2.2 Synthesis of intermediate (**4**)

1. Non-catalytic reaction between benzylamine and bis(2,2,2-trifluoroethyl) carbonate (**3**)

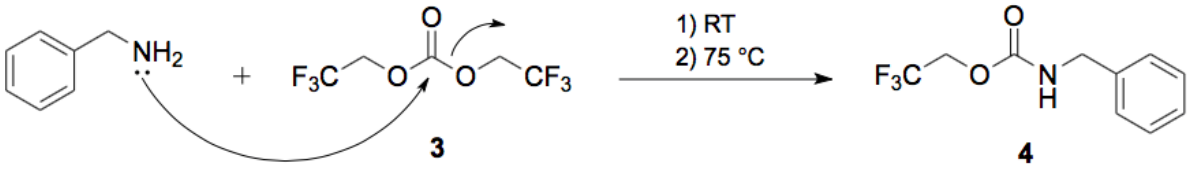


*Figure 67. Non-catalytic synthesis of intermediate (**4**) from benzylamine and bis(2,2,2-trifluoroethyl) carbonate (**3**).*

In a 5 ml round-bottom flask, benzylamine (0.5 mmol, 54.6 µl) and bis(2,2,2-trifluoroethyl) carbonate **3** (0.75 mmol, 112 µl) were added into the 2 ml of acetonitrile (ACN), including stirrer magnet. The mixtures were stirred at the room temperature or 75 °C for 2 hours, 4 hours or overnight. An oil bath was used when stirring at 75 °C. After the reaction, each mixture was transferred into 50 ml measuring flask with 25 µl of mesitylene as an internal standard and diluted with ethyl acetate (EtOAc). The reactions stirred at 75 °C were first cooled down to the room temperature.

For results see chapter *4.3. Results and discussion*.

2. Non-catalytic reaction between aniline and bis(2,2,2-trifluoroethyl) carbonate (**3**)

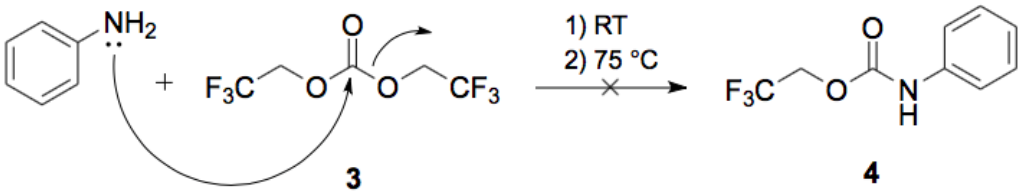


*Figure 68. Non-catalytic synthesis of intermediate (**4**) from aniline and carbonate (**3**).*

In a 5 ml round-bottom flask, aniline (0.5 mmol, 45 µl) and carbonate **3** (0.75 mmol, 112 µl) were added into the ACN (2 ml), including stirrer magnet. The mixtures were stirred at the room temperature or 75 °C for 2 hours, 4 hours or overnight. An oil bath was used when stirring at 75 °C. After the reaction, each mixture was transferred into the 50 ml measuring flask with 25 µl of mesitylene as an internal standard and diluted with EtOAc. The reactions stirred at 75 °C, were first cooled down to the room temperature.

For results see chapter *4.3. Results and discussion*.

3. Catalytic reaction between aniline and bis(2,2,2-trifluoroethyl) carbonate (**3**)

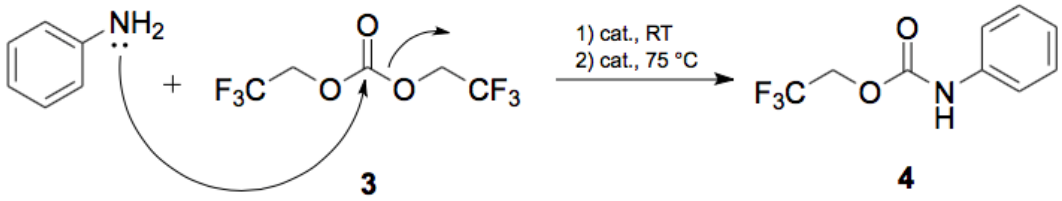


*Figure 69. Catalytic synthesis of intermediate (**4**) from aniline and carbonate (**3**).*

In a 5 ml round-bottom flask, aniline (0.5 mmol, 45.6 µl), carbonate **3** (0.75 mmol, 112 µl) and additional catalysts, DBU (0.05 mmol, 7.5 µl) or DMAP (0.05 mmol, 6.1 mg), were added into the ACN (2 ml), including stirrer magnet. The mixtures were stirred at the room temperature or 75 °C for 2 hours, 4 hours or overnight. An oil bath was used when stirring at 75 °C. After the reaction, each mixture was transferred into the 50 ml measuring flask with 25 µl of mesitylene as an internal standard and diluted with EtOAc, where reactions stirred at 75 °C, were first cooled down to the room temperature.

For results see chapter *4.3. Results and discussion*.

4. Synthesis of intermediate compound **4** from aniline and carbonate **3** with catalyst screening

In a 5 ml round-bottom flask, aniline (0.5 mmol, 45 µl), carbonate (0.75 mmol, 112 µl) and catalysts DBU (0.05 mmol, 7.5 µl) or DMAP (0.05 mmol, 6.1 mg) were added into the ACN (2 ml), including stirrer magnet. The third set was prepared from aniline (0.5 mmol, 45.6 µl) and carbonate **3** (0.75 mmol, 112 µl), mixed in 2 ml of DMF, which had double purpose, i.e. being a catalyst and solvent at the same time. The further steps followed the same procedure as the previous experiment (3).

For results see chapter *4.3. Results and discussion*.

5. Synthesis of intermediate compound **4** from aniline and carbonate **3** with catalyst screening

In a 5 ml round-bottom flask, aniline (0.5 mmol, 45.6 µl) and carbonate **3** (0.75 mmol, 112 µl) were added into the ACN (2 ml), including stirrer magnet. Four different catalysts were additionally added into different flasks; TMG (0.05 mmol, 6.3 µl), DABCO (0.05 mmol, 5.6 mg), TMTU (0.05 mmol, 6.6 mg) or DBU (0.05 mmol, 7.5 µl). The mixtures were first stirred in an oil bath overnight at 75 °C and then cooled down to the room temperature. In the next step, they were transferred into the 50 ml measuring flask with 25 µl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

For results see chapter *4.3. Results and discussion*.

6. Synthesis of intermediate compound 4 from aniline and bis(2,2,2-trifluoroethyl) carbonate (3) with measuring the influence of different solvents (ACN and DMF)

In a 5 ml round-bottom flask, aniline (0.5 mmol, 45 µl) and carbonate **3** (0.75 mmol, 112 µl) were added into the two different solvents, ACN (2 ml) or DMF (2 ml), including stirrer magnet. Two different catalysts, DABCO (0.05 mmol, 5.6 mg) or DBU (0.05 mmol, 7.5 µl), were additionally added. The mixtures were first stirred in an oil bath overnight at 75 °C and then cooled down to the room temperature, transferred into the 50 ml measuring flask with 25 µl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

For results see chapter *4.3. Results and discussion*.

7. Synthesis of intermediate (4) from aniline and bis(2,2,2-trifluoroethyl) carbonate (3) with measuring the influence of dry solvents

Activated molecular sieves were added to both solvents (ACN and DMF) overnight to remove the residual water, which might react with the carbonate and form by-product TFE (Figure 70). After, the reaction method followed the same procedure as in the previous experiment (6).

For results see chapter *4.3. Results and discussion*.

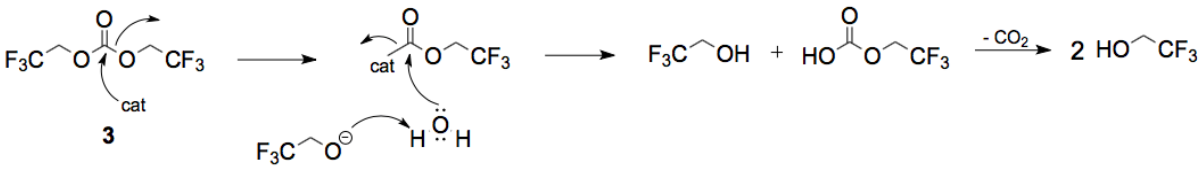


*Figure 70. Reaction between carbonate (**3**) and water in wet solvents.*

8. Synthesis of intermediate (4) from aniline and bis(2,2,2-trifluoroethyl) carbonate (3) under controlled conditions with dry and wet solvents (dry + 20 mol % of H_2O)

Two parallel synthesis were performed at the same time. The first set of synthesis included dry solvents, while the second set included additional 20 mol % of H_2O (2 μl), which was added to the dry solvents. The amount of added carbonate (**3**) was increased to 1 mmol (150 μl). The reaction method followed the same procedure as in the previous experiment (7).

At the end of the optimization process for the first step, 9 samples with the highest intermediate **4** yields obtained, were collected to run ^{1}H NMR and ^{13}C NMR spectra. The reaction mixtures were evaporated under 94 bar, with the water temperature of 40 °C and medium rotation speed for one hour, to remove EtOAc and ACN from the solutions. DMF, DBU and aniline were removed by the extraction with HCl and H_2O. The NMR vial was prepared with the deuterated chloroform $CDCl_3$, used as a solvent.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* = 9 Hz, 2H), 7.35 (dd, *J* = 9 Hz, 2H), 7.11 (t, *J* =7.5 Hz, 1H), 4.56 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 152.05, 137.58, 129.72, 124.77, 119.54, 61.75.

For the other results see chapter *4.3. Results and discussion*.

4.2.3 Synthesis of product 5 from intermediate 4 (Method 1)

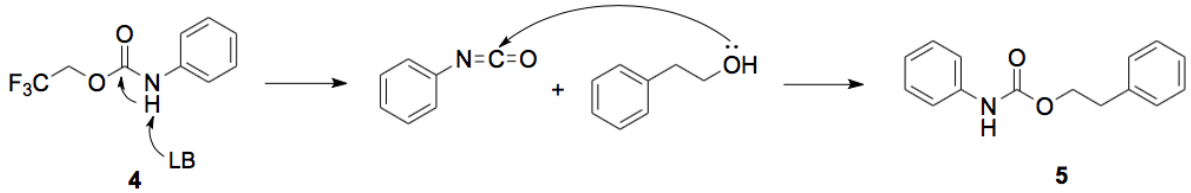


*Figure 71. Synthesis of the product (**5**) from intermediate (**4**) and phenyl ethanol in the second step of optimization process.*

1. Synthesis of product 5 from intermediate 4 and phenyl ethanol and identification of by-product 6

In a 5 ml round-bottom flask, aniline (0.5 mmol, 45.6 μl) and carbonate **3** were added into dried solvents, ACN (2 ml) or DMF (2 ml), including stirrer magnet. Carbonate **3** was added in two different amounts; 0.5 mmol (75 μl) and 1 mmol (150 μl), according to the ratio 1:1 (carbonate **3** : phenyl ethanol) and 1:2 (carbonate **3** : phenyl ethanol). Two different catalysts were additionally added into different flasks; DABCO (0.05 mmol, 5.6 mg) or DBU (0.05 mmol, 7.5 μl). The mixtures were first stirred in an oil bath overnight at 75 °C and then cooled down to the room temperature. In the second step 60 μl of phenyl ethanol (0.5 mmol) was added into each mixture. The solutions were stirred again in an oil bath overnight at 75 °C and then cooled down to the room temperature as before. Mixtures were transferred further into the 50 ml measuring flask with 25 μl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

For results see chapter *4.3. Results and discussion*.

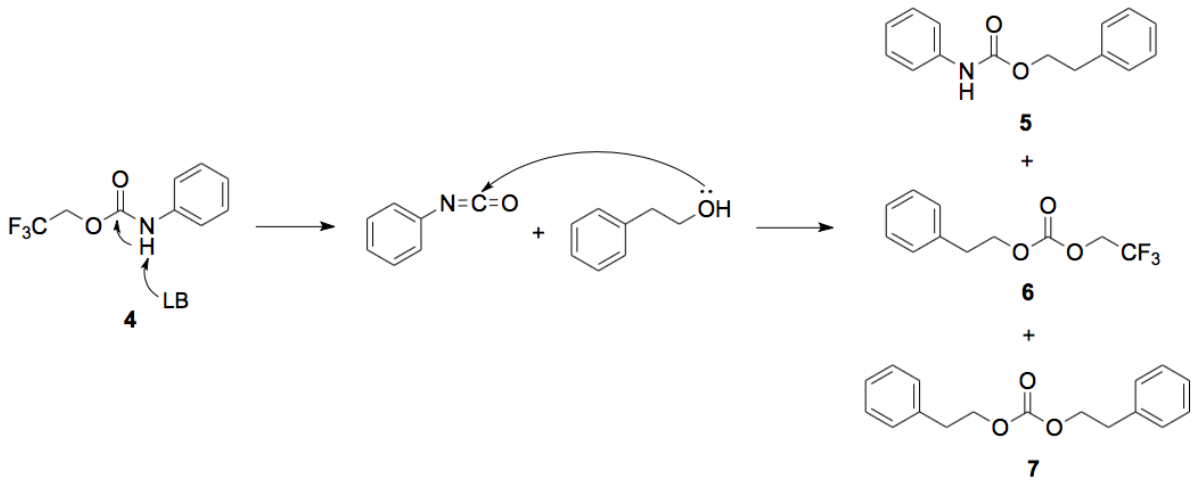
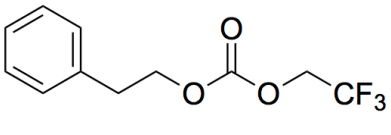
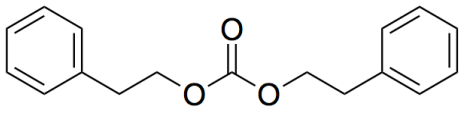


*Figure 72. Synthesis of the product (**5**) from intermediate (**4**) and phenyl ethanol in the second step of optimization process with two additionally obtained structures of by-intermediate (**7**) and by-product (**6**).*

*Table 7. Relative areas to mesitylene of two different structures (by-product (**6**) and by-intermediate (**7**)) after overnight reaction at 75 ℃ in dry solvents (ACN and DMF).*

75 °C, ON	 **6**	 **7**
Ratio 1:1	226.6%	79.3%
Ratio 1:2	226.9%	16.2%

2. Synthesis of product 5 from intermediate 4 and phenyl ethanol with inverse order of addition

The following optimization process was performed in the opposite way as the previous synthesis, starting with the reaction between carbonate and phenyl ethanol in the first step and continuing with adding aniline in the second step.

In a 5 ml round-bottom flask, phenyl ethanol (0.5 mmol, 60 μl) and carbonate **3** (1 mmol, 150 μl) were added to the dry solvents, ACN (2 ml) or DMF (2 ml), including stirrer magnet. Two different catalysts were additionally added into different flasks; DABCO (0.05 mmol, 5.6 mg) or DBU (0.05 mmol, 7.5 μl). The mixtures were stirred in an oil bath overnight at 75 °C and then cooled down to the room temperature. The first set of parallel synthesis was transferred into the 50 ml measuring flasks with 25 μl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

In the second step, 45 μl of aniline (0.5 mmol) was added into each mixture. The solutions were stirred again in an oil bath overnight at 75 °C and then cooled down to the room temperature as before. Mixtures were transferred further into the 50 ml measuring flasks with 25 μl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

For results see chapter *4.3. Results and discussion*.

3. Synthesis of product 5 from intermediate 4 and phenyl ethanol with the increased amount of catalysts

Firstly, aniline (0.5 mmol, 45 μl) and carbonate **3** (1 mmol, 150 μl) were added into two different solvents, ACN (2 ml) or DMF (2 ml), in the 5 ml round-bottom flasks with stirrer magnets. Two different catalysts were additionally added into separated flasks, i.e. DABCO (0.05 mmol, 5.6 mg) or DBU (0.05 mmol, 7.5 μl). The mixtures were stirred in an oil bath overnight at 75 °C and after cooled down to the room temperature.

In the second step, additional amount of catalysts was added into the mixtures at two different temperatures (75 °C and 120 °C). Two parallel synthesis from the first step were implemented in the dry ACN at 75 °C ON, where 50 mol % of DBU (37.5 μl) was added into the first 5 ml round-bottom flask and 50 mol % of DABCO (28 mg) into another one (Table 9). Furthermore, three different parallel synthesis were set up in dry DMF with additional DBU and three more with DABCO. The first synthesis was set at 120 °C overnight with additional 10 mol % of DBU (7.5 μl), the second synthesis at 120 °C overnight with added 50 mol % of DBU (37.5 μl) and the third one at 75 °C overnight with 50 mol % of DBU (37.5 μl) into one 5 mL round-bottom flasks. The same procedure was performed for additional catalyst DABCO (10 mol %, 5.6 mg and 50 mol %, 28 mg).

For results see chapter *4.3. Results and discussion*.

Table 8. The amount of added catalyst (DBU or DABCO) in two different solvents (ACN and DMF) in the second step of the reaction.

	ACN	DMF	DMF	DMF
T (°C)	75	120	120	75
n (mmol)	50	10	50	50

Table 9. The catalytic amount of DBU or DABCO and applied temperature for each sample in two different solvents (ACN and DMF) in the second step.

	DBU/DABCO	DBU/DABCO	DBU/DABCO
ACN	75 °C, 50 mol %		
DMF	120 °C, 10 mol %	120 °C, 50 mol %	75 °C, 50 mol %

4. Synthesis of product **5** from intermediate **4** and phenyl ethanol at three different temperatures and increased catalytic amount

In the first step, aniline (0.5 mmol, 45 μl), carbonate **3** (1 mmol, 150 μl) and 2 ml of dried DMF were mixed in the 5 mL round-bottom flasks with stirrer magnets. The solutions were stirred in an oil bath for 3 hours at three different temperatures (90 °C, 120 °C and 150 °C). Catalyst DBU was added in two different amounts (10 mol %, 7.5 μl and 50 mol %, 37.5 μl) for each temperature. After 3 hours, mixtures were cooled down to the room temperature.

In the second step, 60 μl of phenyl ethanol was added to each 5 ml flask and stirred again overnight at temperatures 90 °C, 120 °C and 150 °C. The next day, mixtures were cooled down to the room temperature, transferred to the 50 ml measuring flasks with 25 μl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

For results see chapter *4.3. Results and discussion*.

Table 10. Reaction conditions with the additional catalytic amount of DBU at three different temperatures.

DBU	90 °C / 120 °C / 150 °C
10 mol %	7.5 μl
50 mol %	37.5 μl

5. Synthesis of product 5 from intermediate 4 and phenyl ethanol at two different temperatures and increased catalytic amount

In the first step, aniline (0.5 mmol, 45 μl), carbonate **3** (1 mmol, 150 μl), catalyst DBU (0.05 mmol, 7.5 μl) and 2 mL of dried DMF were mixed in the 5 mL round-bottom flasks with stirrer magnets. The reactions were set up at 75 °C for 3 hours, using an oil bath. After 3 hours, mixtures were cooled down to the room temperature.

In the second step, 60 μl of phenyl ethanol and additional catalyst DBU in two different amounts (10 mol %, 7.5 μl and 50 mol %, 37.5 μl) were added into 5 ml flasks and stirred again overnight at temperatures 90 °C and 150 °C. The next day, mixtures were cooled down to the room temperature, transferred to the 50 ml measuring flasks with 25 μl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

6. Synthesis of intermediate 4 at three different temperatures in 3-hour reaction time

In the first step of the reaction, aniline (0.5 mmol, 45 μl), carbonate **3** (1 mmol, 150 μl) and 2 ml of dried DMF were mixed in the 5 ml round-bottom flasks with stirrer magnets. The solutions were stirred in an oil bath for 3 hours at three different temperatures (90 °C, 120 °C and 150 °C). Catalyst DBU was added in two different amounts (10 mol %, 7.5 μL and 50 mol %, 37.5 μL) for each temperature. After 3 hours, mixtures were cooled down to the room temperature, transferred to the 50 ml measuring flasks with 25 μl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

For results see chapter *4.3. Results and discussion*.

Table 11. The reaction conditions of experiment 6 with two additional amounts of DBU.

DBU, 3h	90 °C / 120 °C / 150 °C
10 mol %	7.5 μl
50 mol %	37.5 μl

7. Synthesis of product 5 from intermediate 4 at the optimum temperature 120 °C in the first step and additional catalyst in the second step

In the first step, aniline (0.5 mmol, 45 μl), carbonate **3** (1 mmol, 150 μl), catalyst DBU (0.05 mmol, 7.5 μl) and 2 ml of dried DMF were mixed in the 5 ml round-bottom flasks with stirrer magnets. The reactions were set up at 120 °C for 3 hours, using an oil bath. After 3 hours, mixtures were cooled down to the room temperature.

In the second step, 60 μl of phenyl ethanol and additional catalyst DBU (50 mol %, 37.5 μl) were added to the 5 ml flasks and stirred again overnight at temperatures 90 °C, 120 °C and 150 °C. The next day, mixtures were cooled down to the room temperature, transferred to the 50 mL measuring flasks with 25 μl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

For results see chapter *4.3. Results and discussion*.

8. Synthesis of product 5 by repetition of the experiment 7 and additionally evaporated solvent

In the first step, aniline (0.5 mmol, 45 μl), carbonate **3** (1 mmol, 150 μl), catalyst DBU (0.05 mmol, 7.5 μl) and 2 ml of dried DMF were mixed in the 5 ml round-bottom flasks with stirrer magnets. The reactions were set up at 120 °C for 3 hours, using an oil bath. After 3 hours, mixtures were cooled down to the room temperature. In the final step, each flask was evaporated at 94 bar for 15 minutes.

In the second step, 60 μl of phenyl ethanol and additional dried solvent DMF were added to the 5 ml flasks and stirred again overnight at temperatures 90 °C, 120 °C and 150 °C. The next day, mixtures were cooled down to the room temperature, transferred to the 50 ml measuring flasks with 25 μl of mesitylene as an internal standard and filled up with EtOAc till the graduation mark.

For results see chapter *4.3. Results and discussion*.

4.2.4 Synthesis of product **5** from phenyl isocyanate (Method 2)

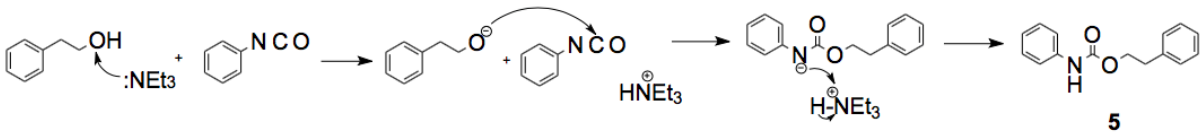


*Figure 73. Synthesis of product (**5**) from phenyl isocyanate and phenyl ethanol.*

Phenyl isocyanate (10.05 mmol, 1.1 ml) and phenyl ethanol (6.7 mmol, 0.8 ml) were added to 50 ml of dichloromethane (DCM) in a Schlenk tube with capacity of 250 ml. While stirring, 0.4 ml of triethylamine was slowly, dropwise, added to the solution. The reaction mixture was continuously stirred for 2 hours at temperature 0-5 °C, using ice bath, and then stirred overnight at room temperature. The next day, 3 ml of concentrated HCl and 4 ml of H_2O were added to the solution. The mixture was transferred to the 50 ml of DCM in the separatory funnel. After the extraction, the solution was dried over $MgSO_4$ for 3 hours, filtered, flushed with additional DCM and evaporated. The mixture was recrystallized further from ether-hexane and dried *in vacuo* overnight. White crystals of product **5** were obtained, giving mass of 0.875 g with 54% yield. GC vial was prepared by dissolving crystals in DCM and diluting them in EtOAc. ^{1}H NMR and ^{13}C NMR were analyzed in $CDCl_3$. FT-IR spectrum was recorded in the solid state.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.22 (m, 9H, Ar-H), 7.04 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.64 (s, 1H), 4.37 (t, *J* = 7.5 Hz, 2H), 2.97 (t, *J* = 6 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 153.60, 137.93, 129.13, 128.65, 126.71, 123.56, 118.89, 65.73, 35.51. IR (cm^{-1}): 3353, 3033, 3972, 2992, 1947, 1878, 1807, 1700, 1597, 1519, 1471, 1441, 1300, 1315, 1222, 729, 619.

For the other results see chapter *4.3. Results and discussion*.

4.2.5 Synthesis of bis(2,2,2-trifluoroethyl) carbonate (**3**)

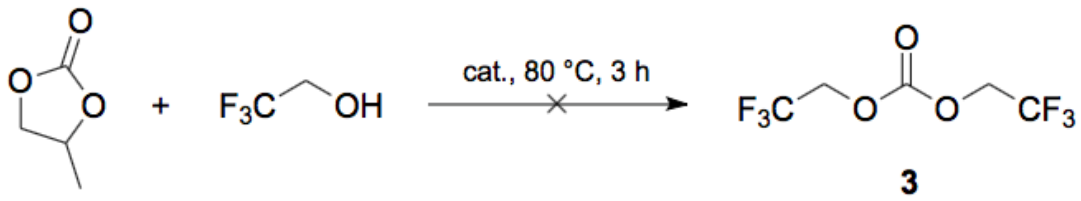


*Figure 74. Attempted synthesis of carbonate (**3**) from propylene carbonate and TFE.*

All metallic salts were weighed and transferred to 5 ml round-bottom flasks, then 1.44 ml of TFE, 0.17 ml of propylene carbonate and stirrer were added to each flask. The mixtures were stirred in an oil bath for 3 hours at 80 °C, diluted with EtOAc in the 50 ml volumetric flask and mixed with the 100 μl of mesitylene. Then 1.11 ml of the solution was transferred from each flask into 10 ml measuring flasks and diluted with the EtOAc again. All GC vials were filled with approximately 1 ml of prepared solutions, which were additionally filtered to avoid contamination from the metallic salts. GC vials were analyzed by the GC-MS technique.

For results see chapter *4.3. Results and discussion*.

*Table 12. List of used catalysts and their amounts for the synthesis of carbonate **3**.*

Catalysts	n (mmol)	M (g/ mol)	m (mg)
$Fe(OTf)_3$	0.02	514.82	10.3
$Cr(OTf)_3$	0.02	507.996	10.2
$Al(OTf)_3$	0.02	482.98	9.7
$Ti(OTf)_4$	0.02	655.87	13.1
$Hf(OTf)_4$	0.02	786.49	15.7

Table 13. Initial reagents in ratio 1:10 (propylene carbonate : TFE*) for the synthesis carbonate **3**.*

Reagents	n (mmol)	ρ (g/ml)	M (g/mol)	V (ml)
Propylene carbonate	2	1.205	102.09	0.17
TFE	2	1.39	100.04	1.44

4.3. Results and discussion

4.3.1 Synthesis of intermediate (**4**)

1. Non-catalytic reaction between benzylamine and bis(2,2,2-trifluoroethyl) carbonate (**3**)

The formation of intermediate **4** was confirmed by the GC-MS analytical method. Therefore, the obtained results of relative areas to mesitylene at room temperature (RT) and 75 °C show that aliphatic amines are reactive enough to synthesize carbamate intermediate **4** with the carbonate **3** in the absence of catalyst.

*Table 14. Relative areas to mesitylene of intermediate **4** after the reaction between benzylamine and carbonate **3** without additional catalyst.*

RT	247.9%
75 °C	305.2%

2. Non-catalytic reaction between aniline and bis(2,2,2-trifluoroethyl) carbonate (**3**)

GC-MS results show no formation of intermediate **4** from no obtained relative areas to mesityilene of carbamate intermediate **4** at RT nor 75 °C. Thus, the experiment confirms that non-activated aromatic amines are not reactive enough to form a desired intermediate **4** with the carbonate **3**, due to delocalized aromatic electrons. Hence, all further reactions with the aniline were performed under catalytic conditions.

*Table 15. No obtained relative areas to mesitylene of intermediate **4** after the reaction between aniline and carbonate **3** without additional catalyst.*

RT	/
75 °C	/

3. Catalytic reaction between aniline and bis(2,2,2-trifluoroethyl) carbonate (**3**)

Obtained GC-MS measurements are showing catalytic and temperature effects on the intermediate **4** yields after 2-hour reaction time. DBU shows stronger catalytic properties than DMAP. However, the strongest impact on the intermediate **4** yield was obtained from the combination of increased temperature and the presence of catalyst DBU.

*Table 16. Calculated yields from the intermediate **4** relative areas to mesitylene.*

	DMAP	DBU
RT	/	5.1%
75 °C	2.7%	21.9%

4. Synthesis of intermediate compound **4** from aniline and carbonate **3** with catalyst screening

Achieved results demonstrate the influence of the longer reaction time, increased temperature and the influence of each catalyst. Therefore, overnight reactions showed stronger impact than 4-hour reaction time, when exposed to the same temperature, i.e. RT. Moreover, the elevated temperature provides even better results by giving the highest yield with the catalytic amount of DBU. To conclude, the temperature has a larger impact on the reaction than time.

No intermediate **4** was obtained with the additional catalyst DMF. By having a closer look in the literature, this result confirms that DBU and DMAP are much stronger Lewis base catalysts than DMF.[125] Moreover, when comparing DMAP and DBU, the latter provides better yields, due to its even stronger Lewis base properties.[126] Hence, in the following synthesis DMF was used only as a solvent.

*Table 17. The yields of intermediate **4** under different temperatures, reaction times and catalysts.*

	DMAP	DBU	DMF
RT, 4h	0.8%	8.2%	/
75 °C, 4h	2.7%	28.3%	/
RT, ON	2.1%	17.4%	/

5. Synthesis of intermediate compound **4** from aniline and carbonate **3** with catalyst screening

DBU and DABCO are two best working catalysts, as shown from the Table 19, where the final results confirm their strong nucleophilicity.[127]

Table 18. The amount of used catalysts in the experiment 5.

	DBU	TMG	DABCO	TMTU
mass/ volume	*7.5* µl	*6.3* µl	*5.6 mg*	*6.6 mg*

*Table 19. Yields of intermediate **4** after overnight reaction at 75 °C with the additional catalysts.*

	DBU	TMG	DABCO	TMTU
75 °C, ON	48.7%	1.8%	66.6%	/

6. Synthesis of intermediate compound 4 from aniline and bis(2,2,2-trifluoroethyl) carbonate (3) with measuring the influence of different solvents (ACN and DMF)

As mentioned in the experiment 4, DMF has been evaluated as a possible solvent besides ACN. The results are showing similar efficiency, where DABCO works best in ACN and DBU in DMF.

*Table 20. Yields of intermediate **4** after overnight reaction at 75 ℃ in two different solvents, ACN and DMF.*

75 °C, ON	DBU	DABCO
ACN	41.4%	52.4%
DMF	51.0%	42.9%

7. Synthesis of intermediate (4) from aniline and bis(2,2,2-trifluoroethyl) carbonate (3) with measuring the influence of dry solvents

Activated molecular sieves were used as dehydrating agents to selectively remove water from both solvents (ACN and DMF). Better yields were obtained with the stronger Lewis base catalyst DBU.[128] The lower yields in wet solvents might be explained by the reaction between the nucleophilic water and carbonate **3**, forming TFE and carbon dioxide. Consequently, less amount of carbonate **3** reacts with the aniline to form intermediate **4**.

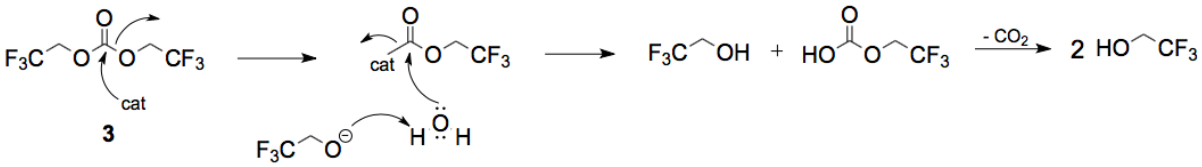


*Figure 75. Reaction between carbonate (**3**) and water in wet solvents.*

Moreover, when comparing the difference of intermediate **4** yields of wet and dry ACN and DMF (in experiment 6 and 7), it could be seen that DMF is less disturbed by the presence of water.

*Table 21. Yields of intermediate **4** after overnight reaction at 75 ℃ in two different dry solvents, ACN and DMF.*

75 °C, ON	DBU	DABCO
ACN	66.0%	37.2%
DMF	59.7%	40.1%

8. Synthesis of intermediate (4) from aniline and bis(2,2,2-trifluoroethyl) carbonate (3) under controlled conditions with dry and wet solvents (dry + 20 mol % of H_2O)

The reactions were performed with dry and wet solvents, where the latter included controlled amount of H_2O (20 mol %), which was added to the dry solvents. Furthermore, wet solvents confirm the influence of present water on the reaction with carbonate **3**, while dry solvents show stronger interactions between carbonate **3** and aniline, by giving greater intermediate **4** formation. Higher yield was also obtained in the presence of catalyst DBU, which confirms better catalytic selectivity.

Additionally, a change of color was obtained, going from colorless into yellow. The two strongest color changes appeared with DBU in dry and wet DMF.

*Table 22. Yields of intermediate **4** after overnight reaction at 75 °C in dry and wet solvents, ACN and DMF.*

75 °C, ON	DBU	DABCO
dry ACN	49.3%	39.6%
dry DMF	23.4%	29.5%
wet ACN	54.7%	25.2%
wet DMF	40.0%	14.0%

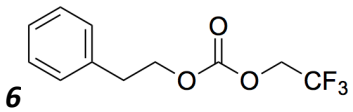
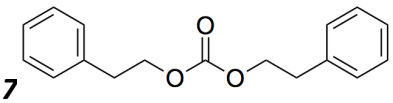
Overall, the results from the optimized first step showed that additional catalyst must be provided in the reaction of intermediate **4** formation from aromatic amine. The highest intermediate **4** yields were obtained at temperature 75 °C in the overnight reaction, with DBU, shown as the most selective catalyst among all the used ones. The most promising catalyst-solvent relation was obtained from DBU in dry DMF.

4.3.2 Synthesis of the product 5 from intermediate 4 (Method 1)

1. Synthesis of product 5 from intermediate 4 and phenyl ethanol and identification of by-product 6

Two additional structures, **6** and **7**, were obtained next to the final product **5** after adding phenyl ethanol. One of them had very similar retention time as the product **5** and the other one as the intermediate **4**. Therefore, two different ratios of phenyl ethanol and carbonate **3** were performed (Table 23), to obtain better selectivity and to successfully distinguish between both structures. Ratio 1:1 confirms that structure **7** reacts preferably when the amount of carbonate **3** and phenyl ethanol is equivalent. Consequently, the alcohol attaches equally on the both sides. Contrarily, structure **6** prefers ratio 1:2, which was confirmed from GC-MC results. To conclude, structure **6** represents the by-product with the retention time 7.48 min^{-1}, close to the final product **5**.

*Table 23. Relative areas to mesitylene of two different structures; by-product (**6**) and by-intermediate (**7**) after overnight reaction at 75 ℃ in dry solvents, ACN and DMF.*

75 °C, ON	**6** 	**7** 
Ratio 1:1 phenyl ethanol (0.5 mmol) : carbonate **3** (0.5 mmol)	226.6%	79.3%
Ratio 1:2 phenyl ethanol (0.5 mmol) : carbonate **3** (1 mmol)	226.9%	16.2%

2. Synthesis of product 5 from intermediate 4 and phenyl ethanol with inverse order of addition

The purpose of this synthesis optimization step was, to possibly obtain higher yield of the final carbamate **5** by changing the order of amine and alcohol in the addition. Therefore, phenyl ethanol was added in the first step of the reaction, to check its reactivity with carbonate **3** and to obtain their main formed intermediate compound **4**. On the other hand, aniline was added in the following second step of the reaction to obtain the final product **5**. Therefore, two sets of the reactions were set up as shown in the Table 24. The first set (1-4) revealed that the main product **5** after the first step was by-product **6**, which again confirms that it is mainly formed with the ratio 1 : 2 between phenyl ethanol (0.5 mmol) and carbonate **3** (1 mmol).

In conclusion, no final product **5** was obtained after the second step. Therefore, the results clearly show an unsuccessful method of the inverse reaction to form the final product **5**.

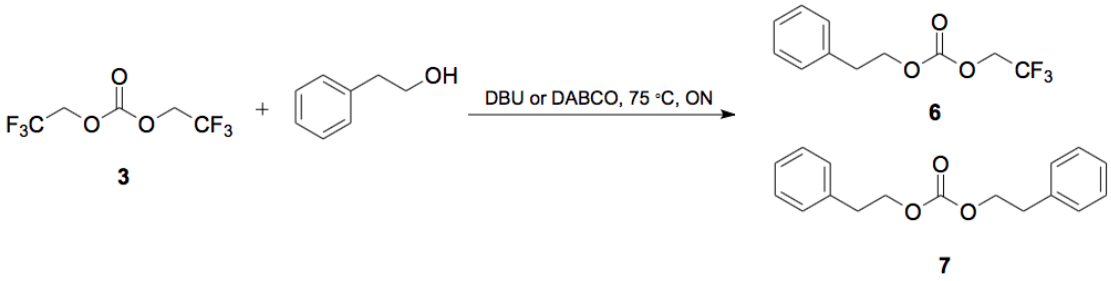


*Figure 76. Synthesis of by-intermediate (**7**) and by-product (**6**) in the inverse reaction of the first step.*

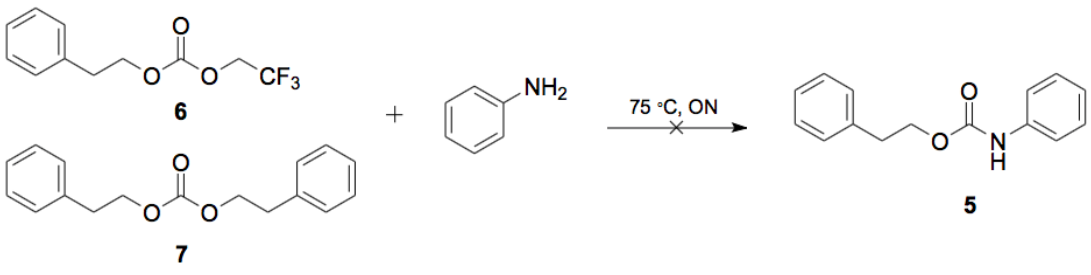


*Figure 77. No obtained product (**5**) in the inverse reaction of the second step.*

Table 24. Two parallel sets of reaction performed at 75 ℃ overnight in dry solvents, ACN and DMF.

75 °C, ON	DBU	DABCO
Dry ACN	1, 5	2, 6
Dry DMF	3, 7	4, 8

*Table 25. Relative areas to mesitylene of by-product (**6**) from added phenyl ethanol in the first step of overnight reaction at 75 ℃ in dry solvents, ACN and DMF.*

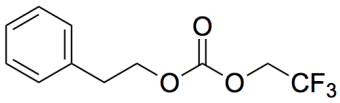
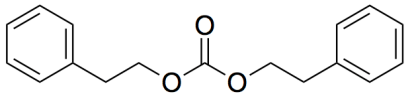
6 	DBU	DABCO
Dry ACN	266.9%	253.0%
Dry DMF	244.5%	320.9%

*Table 26. Relative areas to mesitylene of by-intermediate (**7**) from added phenyl ethanol in the first step of overnight reaction at 75 ℃ in dry solvents, ACN and DMF.*

7 	DBU	DABCO
Dry ACN	10.4%	2.6%
Dry DMF	11.8%	3.4%

3. Synthesis of product 5 from intermediate 4 and phenyl ethanol with the increased amount of catalysts

Additional amount of catalysts (10 mol % and 50 mol %) was added in the second step of the reaction, at temperatures 75 °C and 120 °C. GC-MS results displayed high amount of remaining intermediate **4** and low product **5** yield with the catalyst DABCO. The opposite results were obtained with DBU. Therefore, it can be concluded that DABCO prefers the intermediate **4** formation in the first step nucleophilic reaction, while DBU prefers the product **5** formation in the second step, as a stronger Brønsted base. Hence, DBU is the main driving force in the second step of the reaction.

Table 27. The amounts of added catalyst (DBU or DABCO) in two different solvents (ACN and DMF) in the second step of the reaction.

	ACN	DMF	DMF	DMF
T (°C)	75	120	120	75
n (mmol)	50	10	50	50

Table 28. The catalytic amounts of DBU or DABCO and applied temperature for each sample in two different solvents (ACN and DMF) in the second step.

	DBU/DABCO	DBU/DABCO	DBU/DABCO
ACN	75 °C, 50 mol %		
DMF	120 °C, 10 mol %	120 °C, 50 mol %	75 °C, 50 mol %

*Table 29. Yields of intermediate **4** after the second step of the reaction with increased temperature or increased catalytic amount of DBU or DABCO.*

	DBU	DABCO
ACN (75 °C, 50 mol %)	59.3%	102.5%
DMF (120 °C, 10 mol %)	12.3%	27.3%
DMF (120 °C, 50 mol %)	5.6%	11.4%
DMF (75 °C, 50 mol %)	49.0%	113.1%

*Table 30. Yields of the product **5** after the second step of the reaction with increased temperature or increased catalytic amount of DBU or DABCO.*

	DBU	DABCO
ACN (75 °C, 50 mol %)	1.6%	/
DMF (120 °C, 10 mol %)	19.3%	9.7%
DMF (120 °C, 50 mol %)	18.7%	15.4%
DMF (75 °C, 50 mol %)	2.4%	/

4. Synthesis of product 5 from intermediate 4 and phenyl ethanol at three different temperatures and increased catalytic amount

The only catalyst used in this experiment was DBU, previously shown as the most selective one. Higher amount of added DBU gives greater quantity of the final product **5**. Not only catalyst, but also temperature has an influence on the yield by giving the great results at 120 °C. Consequently, 50 mol % of DBU and temperature 120 °C gave the best results. Additionally, the color change was obtained, switching from colorless to yellow at 90 °C and to dark brown at temperatures 120 °C and 150 °C. Furthermore, when the yield of the product **5** increased, intermediate **4** yield decreased, however, not in the same proportion. Moreover, intermediate **4** yields decreased more drastically then product **5** yields increased. Hence, side reactions have been occurred by giving a strong GC-MS peak of by-product **6**.

Table 31. Added amounts of catalyst DBU at three different temperatures.

DBU	90 °C / 120 °C / 150 °C
10 mol %	7.5 µl
50 mol %	37.5 µl

Table 32. Color changes after the second step with additional 10 mol % and 50 mol % of DBU.

	90 °C	*120 °C*	*150 °C*
10 mol %	*yellow*	*dark brown*	*brown*
50 mol %	*orange*	*dark brown*	*dark brown*

*Table 33. Yields of intermediate **4** after the second step of the reaction under different temperatures or amounts of the catalyst DBU in the dry solvent DMF.*

	90 °C	120 °C	150 °C
10 mol %	70.1%	29.8%	2.0%
50 mol %	44.6%	17.1%	/

*Table 34. Yields of product **5** after the second step of the reaction under different temperatures or amounts of the catalyst DBU in the dry solvent DMF.*

	90 °C	120 °C	150 °C
10 mol %	2.8%	11.0%	15.4%
50 mol %	14.7%	20.8%	14.3%

5. Synthesis of product 5 from intermediate 4 and phenyl ethanol at two different temperatures and increased catalytic amount

The first step of the reaction was set up at the initial temperature 75 °C, while the second step was assembled at temperatures 90 °C and 150 °C with two additional amounts of catalyst DBU (10 mol %, 50 mol %). Comparing to the experiment 4, where the initial temperatures were higher (90 °C, 120 °C and 150 °C), obtained yields of **4** there were understandably better, since already proved from the previous results that the increased temperatures provide stronger reaction reactivity. After the second step, the intermediate **4** showed much lower yields at temperature 150 °C, showing that it did not react just with the alcohol, but it was also effected by other side reactions. Additionally, color changes were obtained, giving stronger and darker colors with the higher product **5** yields (10 mol % and 50 mol % at 150 °C).

Table 35. Changes of color solutions under two different temperatures and amounts of catalyst DBU in the dried solvent DMF.

	90 °C	150°C
10 mol %	Light orange	Dark brown
50 mol %	Light orange	Dark brown

*Table 36. Yields of intermediate **4** after the second step of the reaction under two different temperatures and amounts of catalyst DBU in the dried solvent DMF.*

	90 °C	150 °C
10 mol %	42.7%	1.5%
50 mol %	25.1%	/

*Table 37. Yields of product **5** after the second step of the reaction under two different temperatures and amounts of catalyst DBU in the dried solvent DMF.*

	90 °C	150 °C
10 mol %	5.6%	23.7%
50 mol %	9.2%	14.7%

6. Synthesis of intermediate 4 at three different temperatures in 3-hour reaction time

Synthesis were performed under two different amounts of DBU (10 mol %, 50 mol %) in the first step, to check their influence on the intermediate **4** formation. The highest obtained yields were in the reaction at 120 °C with 10 mol % of catalyst DBU and at 90 °C with 50 mol %. Since higher temperatures increase reaction reactivity, it may also increase the amount of side reactions. Therefore, this might explain why the highest temperature does not necessarily provides the highest yields. Moreover, by comparing relative areas to mesityilene of aniline and intermediate **4** yields, it can be acquired that lower remained amount of aniline does not proportionally gives increased intermediate **4** yields. In conclusion, aniline might be as well under the influence of the other side reactions and consequently forming less intermediate **4** yields.

Table 38. Reaction conditions of experiment 6 with two additional amounts of DBU.

DBU, 3h	90 °C / 120 °C / 150 °C
10 mol %	7.5 µl
50 mol %	37.5 µl

Table 39. Relative areas to mesitylene of aniline after the first step of the reaction under three different temperatures and two different amounts of catalyst DBU in the dry solvent DMF.

	90 °C	120 °C	150 °C
10 mol %	29.0%	/	4.0%
50 mol %	/	5.3%	/

*Table 40. Relative areas to mesitylene of intermediate **4** after the first step of the reaction under three different temperatures and two different amounts of catalyst DBU in the dry solvent DMF.*

	90 °C	120 °C	150 °C
10 mol %	110.8%	112.3%	93.6%
50 mol %	78.2%	53.2%	71.7%

*Table 41. Yields of intermediate **4** after the first step of the reaction under three different temperatures and two different amounts of catalyst DBU in the dry solvent DMF.*

	90 °C	120 °C	150 °C
10 mol %	39.1%	39.7%	33.1%
50 mol %	27.7%	19.0%	25.5%

7. Synthesis of product 5 from intermediate 4 at the optimum temperature 120 °C in the first step and additional catalyst in the second step

The first step was set at the optimized temperature 120 °C for 3 hours with the 10 mol % of added DBU. In the second step, 50 mol % of DBU was added to one set of synthesis. The results of additional DBU (50 mol %) show increased product **5** yield at higher temperature, while the optimum temperature for 10 mol % DBU is obtained at 120 °C. On the contrary, amount of intermediate **4** yields decrease at higher temperatures, which might show the possible correlation with the increased product **5** yield. However, their proportions do not change equally, meaning that intermediate **4** might still be affected by some side reactions.

*Table 42. Yields of intermediate **4** after the second step of the reaction under three different temperatures and added additional amount of catalyst DBU in the dried solvent DMF.*

	90 °C	120 °C	150 °C
10 mol %	43.4%	34.1%	8.6%
50 mol %	29.2%	20.7%	/

*Table 43. Yields of product **5** after the second step of the reaction under three different temperatures and added additional amount of catalyst DBU in the dried solvent DMF.*

	90 °C	120 °C	150 °C
10 mol %	3.3%	7.4%	2.9%
50 mol %	3.7%	3.9%	7.9%

8. Synthesis of product **5** by repetition of the experiment 7 and additionally evaporated solvent

The synthesis followed the same procedure as the previous experiment with the evaporated solvents after the first step. The overall results showed higher amount of product **5** yields, compared to the experiment 7, with the best working temperature at 120 °C. Since DMF is a polar aprotic solvent, it can accept protons. Therefore, its presence might affect the reaction by interacting with intermediate carbamate **4** in the second step and consequently causing lower product **5** formation. In conclusion, the absence of DMF solvent provides beneficial results.

*Table 44. Yields of intermediate **4** after the second step with evaporated solvent DMF.*

	90 °C	120 °C	150 °C
10 mol %	34.6%	/	10.3%
50 mol %	20.6%	7.4%	/

*Table 45. Yields of product **5** after the second step with evaporated solvent DMF.*

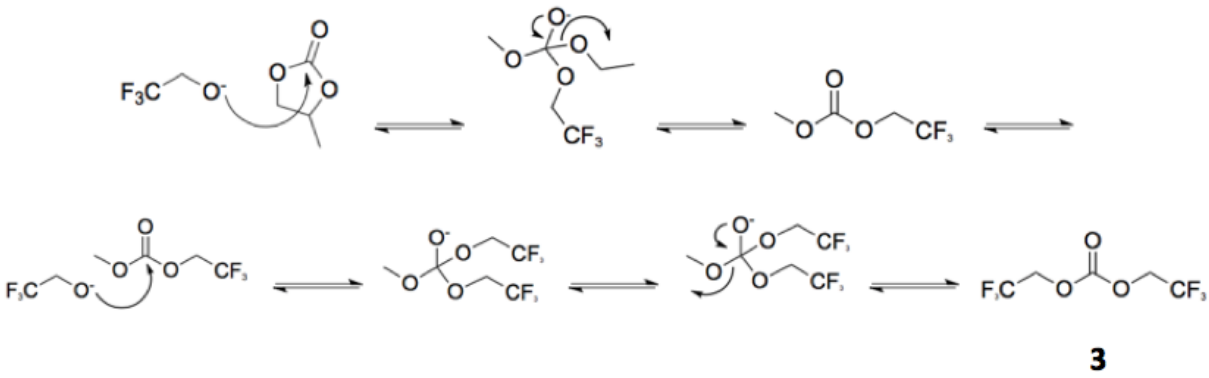
	90 °C	120 °C	150 °C
10 mol %	/	16.3%	14.6%
50 mol %	4.9%	21.2%	3.2%

4.3.3 Synthesis of product **5** from phenyl isocyanate (Method 2)

Additional product **5** synthesis was applied to obtain pure desired carbamate **5** and to quantify its yield. Performed experiment followed procedure *via* isocyanate route, from phenyl isocyanate and phenyl ethanol. Consequently, the reaction provided the final product **5** without any supplemental by-product **6**. The obtained carbamate **5** was analyzed with ^{1}H NMR, ^{13}C NMR and IR spectra.

4.3.4 Synthesis of bis(2,2,2-trifluoroethyl) carbonate (**3**)

Sovent-free transesterification was performed from propylene carbonate and TFE, with the aim of producing carbonate **3** (Figure 78). Reaction was set at 80 °C for 3 hours, under the influence of five different metallic catalysts (0.02 mmol). After the reaction with catalysts $Ti(OTf)_4$, $Cr(OTf)_3$, $Fe(OTf)_3$, the color of reaction mixtures changed (Table 47), while the solution with $Fe(OTf)_3$ turned into yellow even before the reaction (Table 46*)*.



3

*Figure 78. Reaction mechanism of carbonate (**3**) synthesis.*

In conclusion, no product **3** has been obtained. Acquired two peaks from GC-MS spectrum identify initial reagent propylene carbonate with the retention time at 4.70 min and the internal standard mesitylene at 4.48 min. Even though the reactions were conducted under solvent-free conditions to eliminate potential effects of solvent, the overall experiment still failed. However, catalytic activity of the metal triflates might still be improved by increasing oxophilicity and Lewis-acidity.

Table 46. Change of color in metallic salt solutions before the reaction.

Metallic salt	Change of color before added metallic salt	Change of color after added metallic salt
$Fe(OTf)_3$	colorless	yellow

Table 47. Color changes in the metallic salt solutions after the reaction.

Metallic salt	Color before the reaction	Color after the reaction
$Ti(OTf)_4$	colorless	light brown
$Cr(OTf)_3$	colorless	green
$Fe(OTf)_3$	yellow	dark brown/ black

No further reactions were performed, due to the lack of estimated time for experimental part of the Master Thesis.

5. Conclusions

Carbamates have applications since the 19th century, right after their discovery. They are used in the paint industry, in the polyurethane synthesis and in agriculture as pesticides, fungicides and insecticides. Cyclic carbamates have a significantly important role in the medicine and pharmaceutical industry, where their unique structure enables drug and prodrug designing.

Carbamates have been successfully synthesized by the great range of methods. Therefore, three main procedures have been introduced, i.e. *via* phosgene, *via* isocyanate and the reaction with carbon dioxide. The first two methods represent standard techniques including highly toxic phosgene as a starting material. On the other hand, carbamates might be as well synthesized directly from the less toxic isocyanate, yet undesirable procedure. However, the third method represents safer and the environmentally friendlier reaction with nontoxic and noncorrosive carbon dioxide. Thus, this procedure has been established as CO_2 re-cyclization and conversion into useful compounds.

The present work focuses on the optimization of *N*-aryl carbamate synthesis through halide-free pathway. The reaction was performed in two steps under catalytic conditions, using several different parameters, such as temperature, reaction time and different amounts of reagents. The first step of the synthesis consists of a reaction between aromatic amine and carbonate. Due to decreased reactivity of aryl amines by the aromatic ring, catalyst was applied. The reaction of the first step represents nucleophilic catalysis with the attack of electronegative aniline nitrogen towards carbonyl carbon in the carbonate molecule forming intermediate **4**, which reacts further with the alcohol in the second step, forming final carbamate product **5** under catalytic basic conditions.

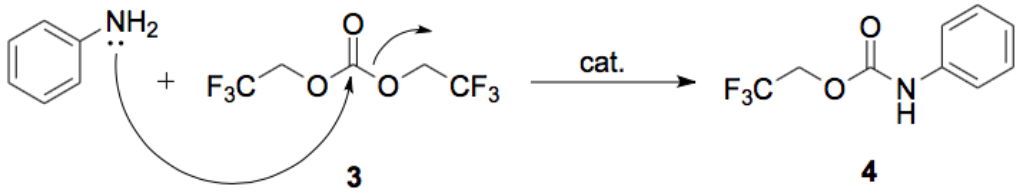


*Figure 79. The first step of the optimized catalytic reaction, forming carbamate intermediate (**4**).*

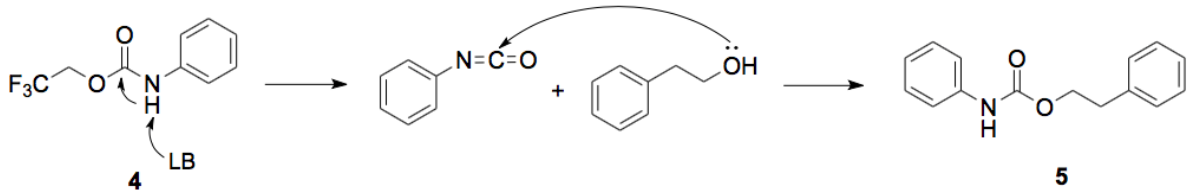


*Figure 80. The second step of the optimized catalytic reaction, forming carbamate product (**5**).*

The results after both optimization steps showed that temperature and increased amount of catalyst provide the highest **5** yields. Despite the fact, that increased temperature usually provides better results, the optimum temperature from the reaction was 120 °C. The higher temperatures generate a greater amount of side reactions and consequently form less **5**. However, the investigated carbamate products **5** have diverse alternative applications, despite the effects of side reactions. On the other hand, increased amount of catalysts provides better yields. Out of all, DBU shows the best catalytic selectivity, due to its strong nucleophilicity and basicity, while other catalysts, e.g. TMTU, have more steric hindrance, which consequently decreases their reactivity. It was shown that applied parameters were effectively optimized in both steps, giving satisfying yields of carbamate intermediate **4** in the first step and the final product **5** yields in the second step.

In conclusion, the alternative approach of presented synthesis usually forms toxic halide acids with harmful environmental effects. Since the main waste product of this work is TFE, it represents halide-free procedure. The second step is representing the phosgene-free pathway through transesterification, forming **5**. To conclude, both steps have been shown as a successful procedure of carbamate formation, avoiding phosgene route, with the overall reaction, shown as an environmentally friendlier and as far more attractive method for various applications.

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7. Appendix

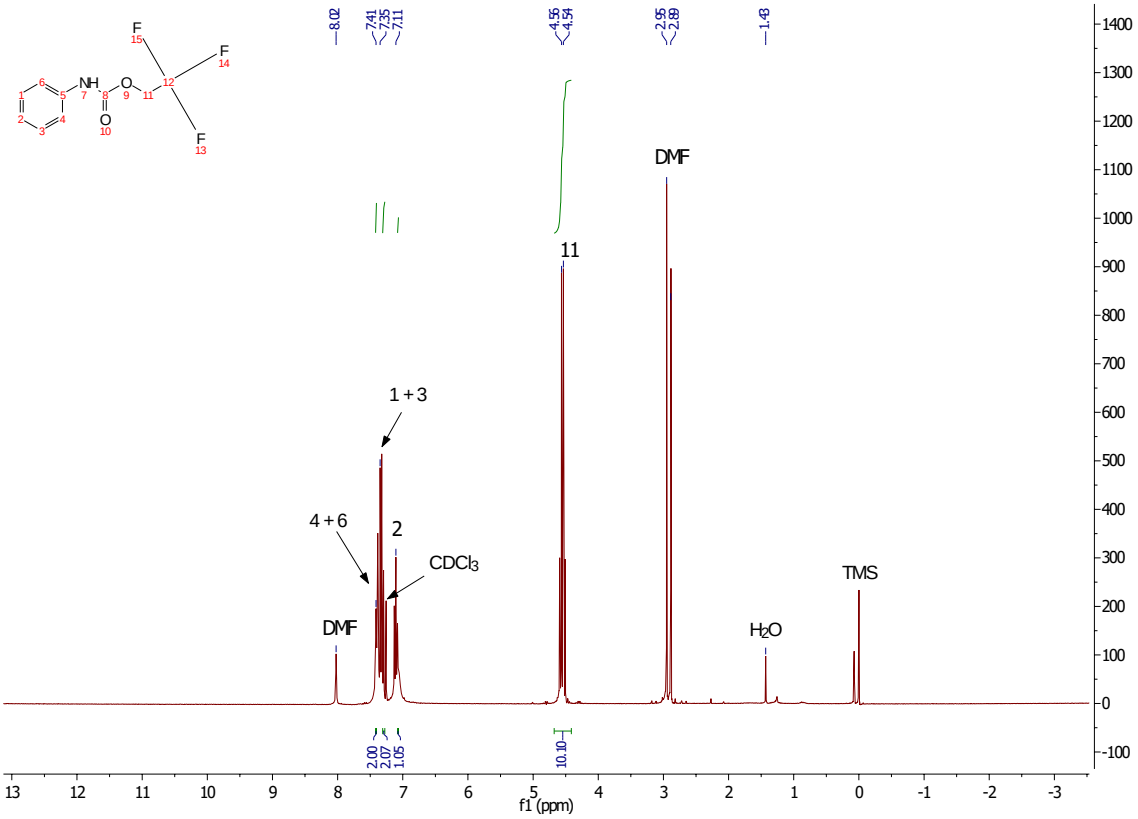

Figure 81. ^{1}H NMR spectrum of the intermediate.

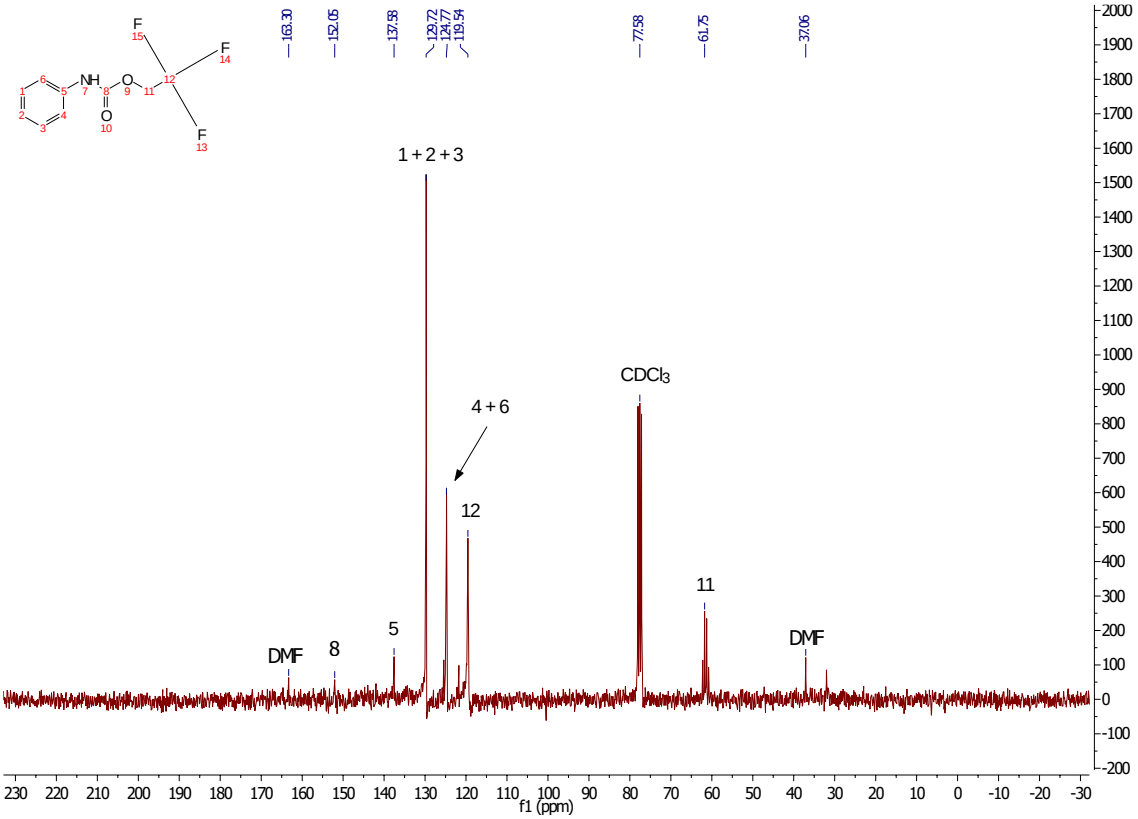

Figure 82. ^{13}C NMR spectrum of the intermediate.

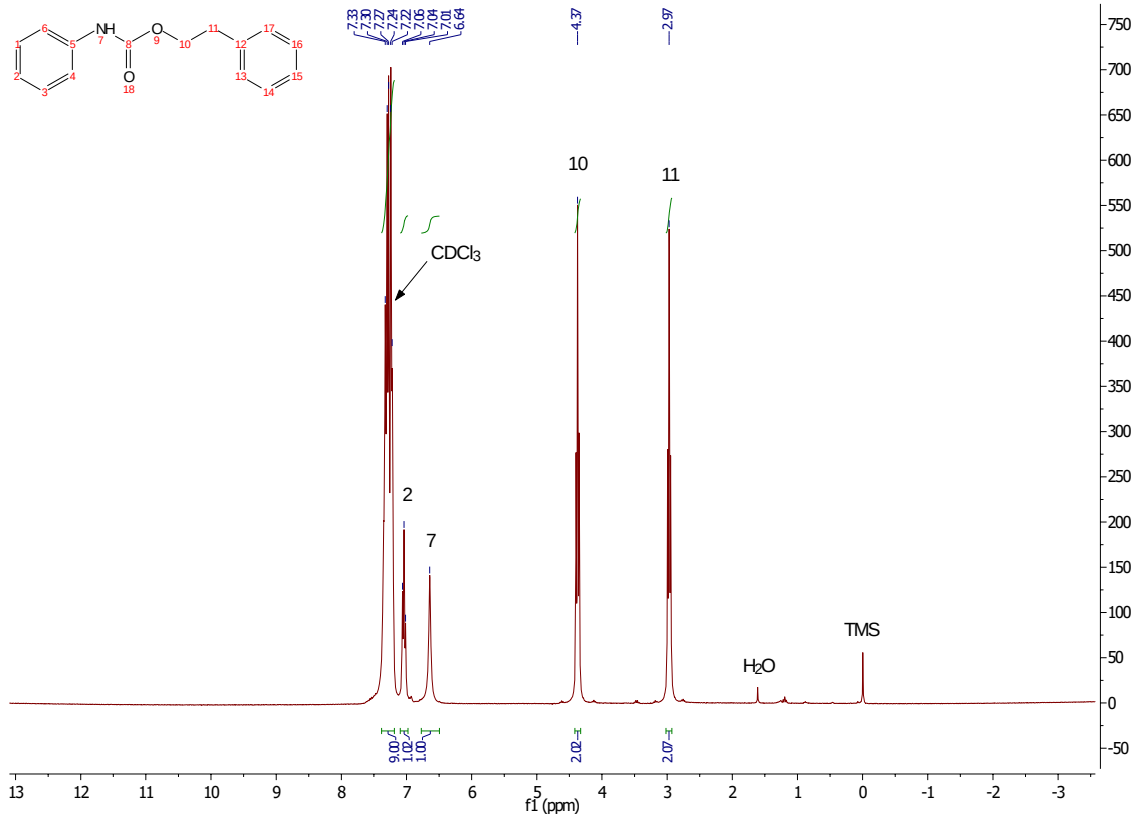

Figure 83. ^{1}H NMR spectrum of the final product.

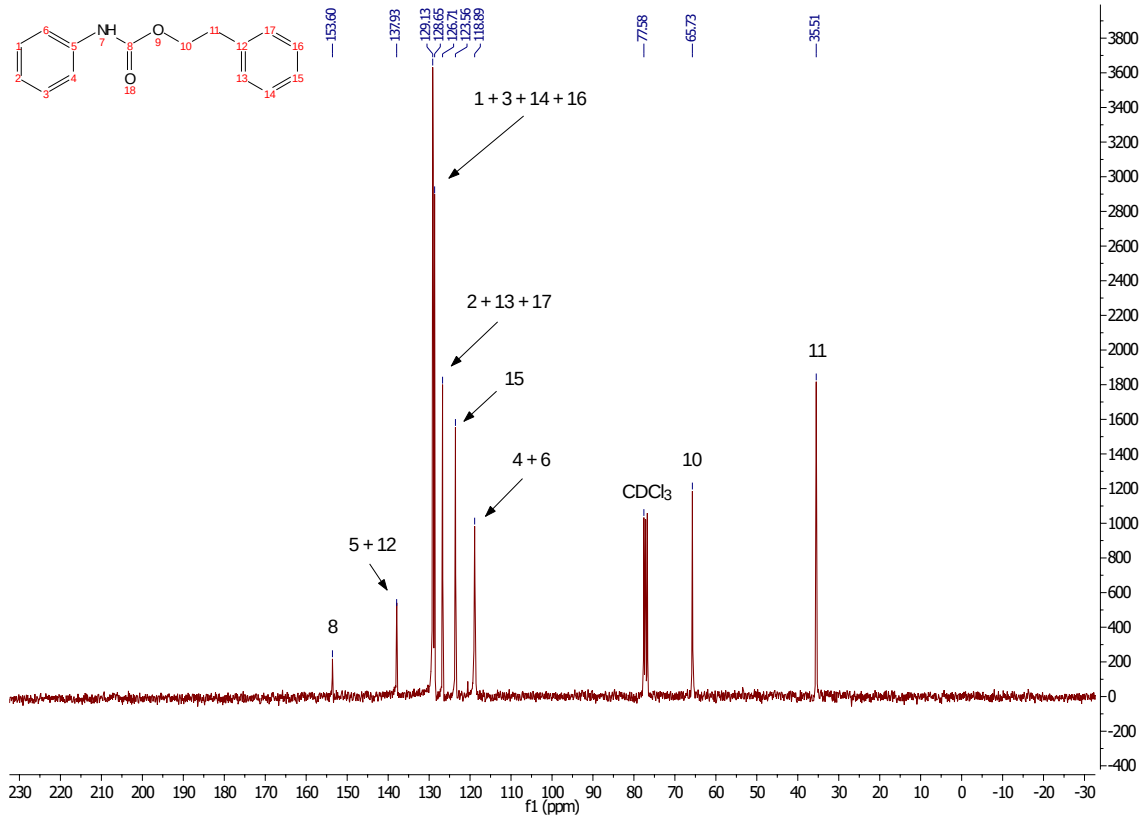

Figure 84. ^{13}C NMR spectrum of the final product.

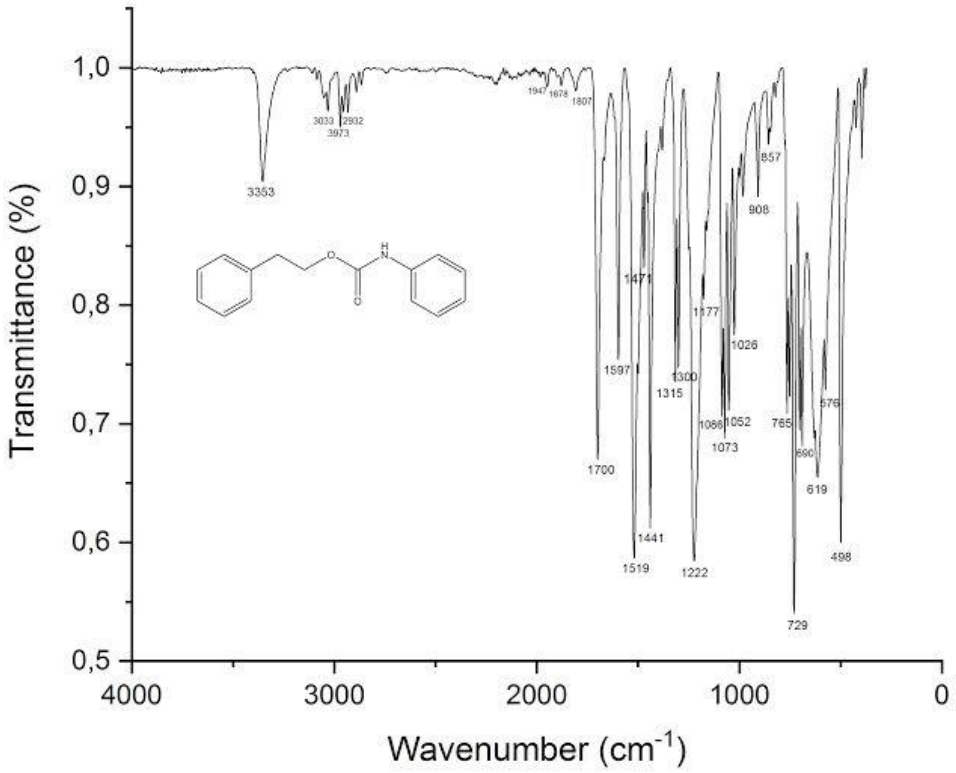

Figure 85. FT-IR spectrum of the final product, recorded on a Bruker ALPHA-P FT-IR spectrometer.

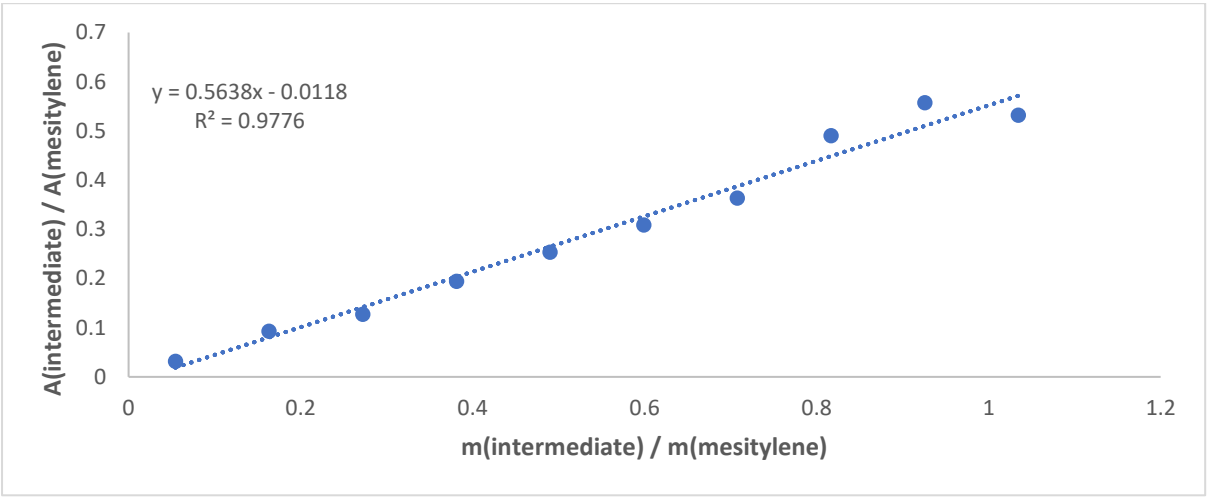

Figure 86. Calibration curve of intermediate.

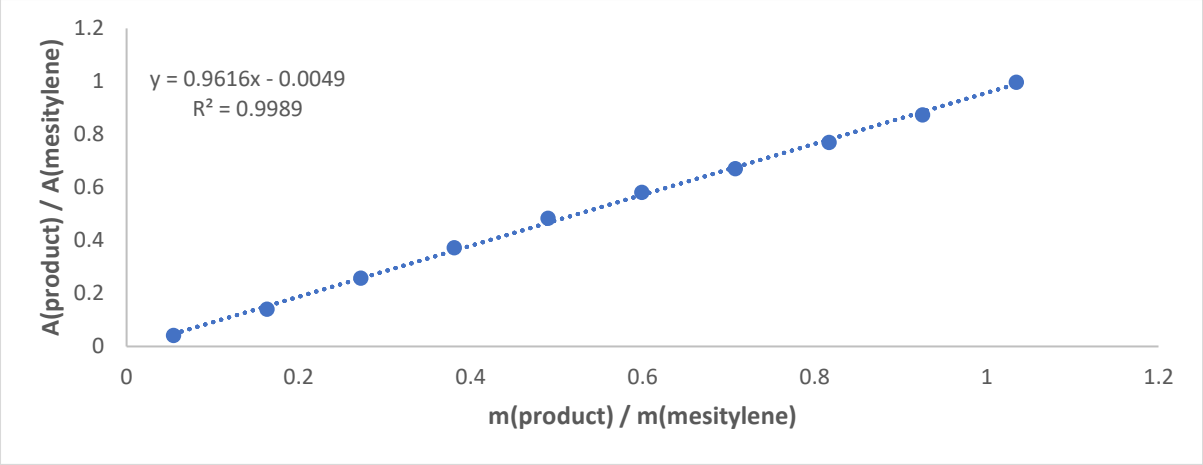

Figure 87. Calibration curve of product.