Synthesis of a new symmetric carbonate with leaving group

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The study of the reactivity of organic reactive carbonates with leaving groups (succinimidyl, phthtalimidyl and norbornenyl) towards oxygen and nitrogen nucleophiles proved to be useful due to the applicability of the resulting compounds in avant-garde fields of chemistry, such as biochemistry and the pharmaceutical industry. This study has been heavily focused on developing new, cleaner, chemical processes using an original method. The goal of this paper is to prepare a new symmetrical reactive carbonate with leaving group by an original method, aimed at reducing chemical residues with a negative impact on the environment and human health. In peptide synthesis, reactive organic carbonates are used especially for the protection of amino groups, by converting it into a carbamate-type derivative through an alkoxycarbonylation reaction, and for the activation of carboxyl groups by converting it into a reactive ester. For the protection of the amino function in amino acids, alkoxycarbonyl-type (carbamate) groups are preferred, which minimize the racemization of optically active centers. In modern peptide synthesis, at the international level, the applications of phthtalimidyl organic carbonates are related to the activation of carboxyl groups in amino acids and peptides. The process of obtaining symmetrical carbonate with leaving group is the starting point for obtaining new amino-protecting groups with special importance in the synthesis of peptides.

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1. Introduction

In the last years, there is a continuous interest regarding the development and implementation of more sustainable chemical technologies to replace toxic reagents, solvents, catalysts, by-products and hazardous-waste products by alternative methods which use eco-friendly solvents [4].

The synthesis of a new compound used as alkoxycarbonilation reagent of amino acids for peptides synthesis is opportune for activation of carboxyl group and for protection of amino group. The symmetrical carbonates with leaving group have various important applications: they are used for the insertion of a carbonyl group between amino, hydroxyl and thio groups for the synthesis of urea, carbamates, dithiocarbamates and isothiocyanates. They can also be used as dehydrating agents, and for the preparation of the reactive esters of the amino acids [5].

The synthesis of biologically active compounds starting from non-toxic and biodegradable chemical compounds of the reactive organic carbonate type by an original procedure is an alternative way to the traditional method, which employs toxic and dangerous reagents (phosgene and its chlorinated derivatives), as well as the applicability of these derivatives to the synthesis of bioactive compounds with many utilizations in pharmaceutics and food industries [9, 10].

Using derivatives of *N*-hydroxisuccinimidyl, *N*-hydroxiphtalymidyl and dibornenyl in order to obtain active esters from amino acids in modern peptide synthesis is one of the most used methods for activation.

The activation method using symmetrical carbonates of *N*-succinimidyl and *N*-phtalymidyl proved to be beneficial, because it is a simple method, very efficient, requires mild reaction conditions, and does not lead to racemization of the amino acid [5]. The main advantages of this type of organic carbonates are the reduction of emissions of toxic chemicals and the extension of the use of renewable resources. Beside the product, symmetric carbonates are obtained only from carbon dioxide and *N*-hydroxysuccinimide, *N*-hidroxyphtalymide, *N*-hydroxi-5-norbornene-2,3-dicarboximide, which can be easily removed from the reaction medium [5,7,8].

Concerning peptide synthesis, symmetric carbonates play an important role because they are easily accessible; inhibit the racemization during the activation and coupling phase; the *N*-hydroxyimidic derivatives present nucleofuge-like behavior in the nucleophilic substitution reactions, due to their resonance withdrawing effect [2].

In this paper the preparation of a new symmetrical reactive carbonate with leaving groups by an original procedure will be investigated.

Traditional methods used for introducing the carbonyl group use phosgene or carbonyl diimidazole, which is either toxic or expensive. In contrast, organic carbonates

with leaving group are less toxic, easy to handle and inexpensive as reagent for introducing the carbonyl group [6-8].

The new compound can be used as protective group or can act as the condensation agent which is employed directly of peptides from two or more amino acids [1].

2. Materials and methods

2.1. Materials

All reagents were purchased from chemical suppliers and used without further purification.

2.2. Synthesis of symmetrical carbonate

Endo-*N*-hydroxy-5-norbornen-2,3-dicarboximide (550.8 mg, 3.09 mmol) was dissolved in tetrahydrofurane (45 mL), bis (trichloromethyl) carbonate (TPG) (303.0 mg, 1.02 mmol) and tri-*n*-butylamine (1,440 ml, 14.35 mmol) was added. The reaction mixture was stirred at room temperature for 15 minutes. After vacuum solvent evaporation, the residue was dissolved in ethyl acetate (20 ml) and the solution was three time washed with 20% citric acid solution (5 mL), 5% $NaHCO_3$ solution (5 mL) and saturated NaCl solution (5 mL). The organic phase was dried ($MgSO_4$) and concentrated to dryness. The residue was crystallized from acetone.

2.3. Characterisation

2.3.1 FT-IR spectroscopy

The *IR spectra* were recorded in KBr pellet for solid compounds and the reaction monitoring was carried out in thermostated silicon cells of 0.137 mm thickness on a Bruker FT/IR-Vertex 70 instrument.

2.3.2. Mass spectroscopy

Mass spectrometry was conducted on a High Capacity Ion Trap Ultra (HCT Ultra, PTM discovery) mass spectrometer from Bruker Daltonics, Bremen, Germany. HCT MS is interfaced to a PC running the CompassTM 1.2 integrated software package, which includes the HystarTM 3.2.37 and Esquire 6.1.512 modules for instrument controlling and chromatogram/spectrum acquisition, and Data Analysis 3.4.179 portal for storing the ion chromatograms and processing the MS data.

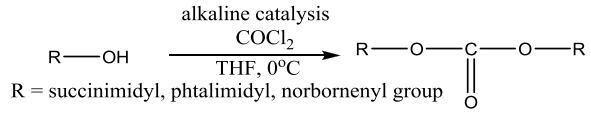
2.3.3. RMN spectroscopy

The *^{1}H-NMR and ^{13}C-NMR* were recorded on a Bruker DPX at 200 MHz in DMSO-*d6*, with TMS as reference. The values of coupling constants are normal for vicinal couplings (CH-CH, CH-NH): 6.5 -7 Hz.

Detailed MS, ^{1}H-NMR and ^{13}C-NMR spectra are available from the authors.

3. Results and discussions

The conventional synthetic method for the obtaining symmetrical carbonates with leaving groups involved the reaction between *N*-hydroxy compounds and diphosgene, in alkaline catalysis, in the presence of a non-polar solvent (THF), as presented in the next reaction scheme (Scheme 1).



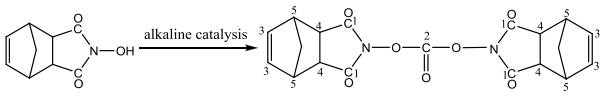
Scheme 1. General synthetic procedure for preparation of reactive organic carbonates with leaving groups.

But, these methods suffer an important main drawback: the presence of toxic reagent (diphosgene) which promote the development a facile synthetic strategy for efficient, convenient, and practical synthesis of symmetrical carbonates with leaving groups. Recently, it was reported a FT-IR study for determination the most appropriate reaction conditions for preparation of this symmetric carbonate [6].

In this paper the procedure for the preparation of reactive symmetric carbonates with leaving groups was investigated[3] using the results of the FT-IR monitoring parameter reaction in order to develop a new efficient synthetic route for symmetrical norbornenyl carbonate starting from endo-*N*-hydroxy-5-norbornen-2,3 dicarboximide [6].

The syntheses are carried out in heterogeneous medium, in the molar ratio endo-N-hydroxy-5-norbornen-2,3-dicarboximide: TPG: amine (TBA) = 1:1:1., at room temperature (25°C) due to the low solubility of the endo-*N*-hydroxy-5-norbornen-2,3-dicarboxyimide in alkaline catalysis (Scheme 2). The yields were high (78%).

Beside the above mentioned method concerning the obtaining of new symmetric organic carbonate *(N,N'*-bis(endo-5-norbornen-2,3-dicarboximidyl) carbonate), was obtained as white solid, by recrystallization from acetone.



Scheme 2. Reaction for obtainainig symmetrical carbonate.

This represent the best reaction conditions found for the preparation of this carbonate.

The confirmation of the final reaction product was achieved through different analysis and characterisation methods: IR spectroscopy, mass spectrometry, RMN spectroscopy.

The IR spectroscopic data were recorded in the 2500-1400 cm^{-1} region, corresponding to the valence vibrations of the carbonyl group.

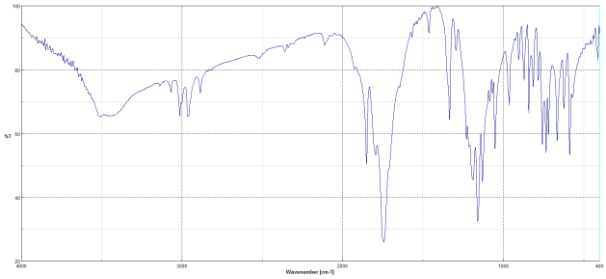


Fig. 1. The FT-Ir spectra of final compound.

IR (KBr pellet, ν(cm^{-1}): 1740.44(C=O), 1795.4(C=O), 1851.33(C=O)
MS (m/z): 74.06, 146.4, 182.6, 291.6, 324.7, 351.8, 376.8, 378.6, 383.2. [Calc. for $C_{19}H_{14}N_2O_7$: requires M, 382.13. Found: 283.2 (M+1)].
^{1}H-RMN (DMSO) (ppm): 6.23m, 3.79q, 3.55d, 3.36m, 1.75m
^{13}C-RMN (DMSO) (ppm): 173.3 (C_1), 153.6 (C_2), 135.9 (C_3), 47.3 (C_4), 45.5 (C_5).
All data for final compound were consistent with the proposed structure.
The symmetrical organic carbonates with leaving group are versatile compounds that represent an attractive eco-friendly alternative for toxic traditionally phosgene substitutes.

4. Conclusions

The synthesis of new symmetrical carbonate with leaving group which may be used in synthesis of compounds with biological activity, by a modern method starting from a coupling reagent used in peptides synthesis, has been succeeded.

The new obtained symmetric organic carbonate with leaving group presents importance because it represents the raw material for the synthesis of new mixed carbonates from primary, secondary or tertiary benzyl alcohols, which can be used as intermediaries used in amino protecting groups.

Acknowledgements

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