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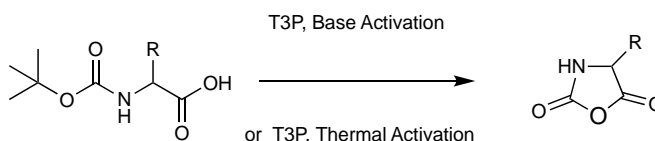
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Synthesis of α -Amino Acid N-Carboxyanhydrides

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ABSTRACT: A simple phosgene- and halogen-free method for synthesizing α -amino acid N-carboxyanhydrides (NCAs) is described. The reaction between Boc-protected α -amino acids and T3P[®] reagent gave the corresponding NCA derivatives in good yield and purity with no detectable epimerization. The process is safe, easy-to-operate and does not require any specific installation. It generates non-toxic, easy to remove by-products. It can apply to the preparation of NCAs for the on-demand on-site production of either little or large quantities.

α -Amino acid-N-carboxyanhydrides (NCAs) (oxazolidinone-2,5-dione derivatives) are cyclic activated amino acid building blocks that are highly reactive with nucleophiles,¹ producing only carbon dioxide as a by-product. This feature has highlighted their usefulness in creating amide bonds.² NCAs are also the main reagents used in the synthesis of well-defined peptide polymers^{3a-c} that have recently grown in importance and are now used in some of the most innovative healthcare strategies⁴ including controlled drug/gene delivery systems, tissue engineering, molecular imaging, and diagnostics.⁵ As an example, Glatimer, which is prepared through the random copolymerization of (L)Ala-NCA, (L)Glu(OBzl)-NCA, (L)Lys(Tfa)-NCA, and (L)Tyr-NCA, is commercially available for the treatment of multiple sclerosis.⁶ NCAs have also been used to produce several active pharmaceutical ingredients e.g., the antiviral drug Saquinavir and Nelfinavir intermediates,⁷ and polypeptide-based polymer therapeutics that are currently in clinical trials including the poly(glutamic acid)-paclitaxel conjugate Opaxio[™] for treating various cancers and the poly(ethylene glycol) methyl ether-poly(aspartic acid)-paclitaxel micelle NK-105 for treating breast cancer.⁸ Poly(glutamic acid) is predicted to become an important biopolymer,⁹ and poly(lysine) and poly(aspartic acid) have been developed for use as carriers, because they have high drug loading capacities and are biodegradable.¹⁰ On the other hand, (L)Leu-NCA is produced industrially for the synthesis of polyleucine, which is used as a catalyst in the Julia-Colonna asymmetric epoxidation method.^{11a-b} NCAs are also useful intermediates for the “green” solvent-free synthesis of peptides.¹²

Leuchs was the first to develop a method for synthesizing α -amino acid NCAs (Leuchs’s anhydrides) by treating N-alkyloxycarbonyl amino acids with halogenating agents (e.g.

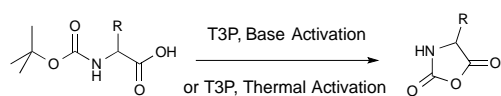
PBr₃, PCl₃, PCl₅, SOCl₂, α,α -dichloromethylmethyl ether), which result in the formation of carcinogenic alkyl halides;^{13a-c} other methods have since been developed. These include the reaction of phosgene with α -amino acids (the Fuchs–Farthing method),^{14a-b} and methods involving a nongaseous phosgene substitute (diphosgene or triphosgene).^{15a-b} A method for synthesizing NCAs using phosgene through basic-to-acidic flash switching in a microflow reactor has recently been described, and allows the synthesis of NCAs bearing acid-labile protecting groups.¹⁶ So far, the most common methods for preparing NCAs involve phosgene, but the high toxicity of phosgene and legal restrictions on its use, which can cause the release of corrosive gaseous HCl, mean that such methods are difficult to start up. Some phosgene-free methods for synthesizing NCAs have been developed to avoid these drawbacks. Some of these methods have involved the use of NO gas and oxalyl chloride,^{17a-b} di-*tert*-butyltricarboxylate,¹⁸ bisaryl carbonates,^{19a-b} and cyanuric chloride.²⁰ Unfortunately, none of these have become popular due to their incompatibility with some protecting groups, the formation of side products, the toxicity of the reactants, and complications due to the large number of steps in the reaction. The Fuchs–Farthing method is still the most widely used for synthesizing NCAs, particularly in industrial settings. There is therefore a clear need for a mild, non-acidic, safe, easy-to-use process for producing a wide range of NCAs in good yields, high purities, based on reagents that are chemically compatible and apparatus that is widely available, and which produces inoffensive by-products that can be removed easily.

n-Propanephosphonic acid anhydride (T3P[®]) has been found to be useful for activating carboxylic acids and forming amide bonds under mild conditions.²¹ T3P[®] is a non-toxic reagent that does not require specific handling measures. It is one of

the most widely used carboxylic acid activating reagents for large-scale syntheses.^{22a-b}

We recently reported an interesting property of T3P[®] in that it can activate carboxylic acids to yield simply and cleanly α -amino acid N-acyl-benzotriazole derivatives²³ that have unexpected reactivities towards weak nucleophiles in acidic media.²⁴ From our study of the synthesis of N-acyl-benzotriazole derivatives, when synthesizing Boc-(*L*)Tyr(OtBu)-OBt from Boc-(*L*)Tyr(OtBu)-OH in the presence of T3P[®], pyridine and benzotriazole, in AcOEt as solvent, we noticed faint traces of a side product that was identified unexpectedly as (*L*)Tyr(OtBu)-NCA. We then performed the reaction using Boc-(*L*)Tyr(OtBu)-OH, 1.2 T3P[®] eq in AcOEt as solvent, under the same experimental conditions, but with no benzotriazole. Surprisingly, some (*L*)Tyr(OtBu)-NCA formed rapidly after a 2 h reaction (Scheme 1).

Scheme 1. Synthesis of NCAs



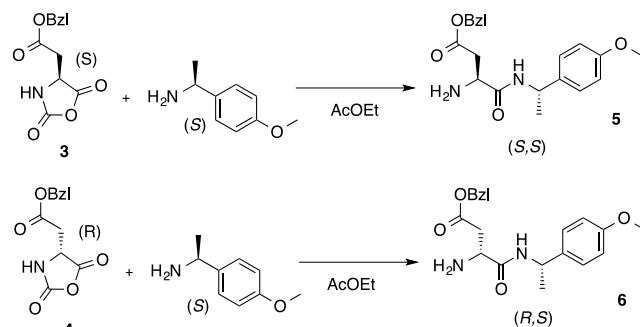
We decided to study this interesting reaction further. We first explored the effect of temperature on the reaction. By increasing the reaction temperature to 50 °C it was possible to achieve a high Boc-(*L*)Tyr(OtBu)-OH conversion rate, and (*L*)Tyr(OtBu)-NCA was isolated with a good yield. We then investigated the use of a base (2 eq) as a “reaction facilitator”, including pyridine, 4-dimethylamino-pyridine, N-methylmorpholine, N,N-diisopropyl ethylamine, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, and the inorganic base K₂CO₃. Each reaction was performed at room temperature for 2 h using EtOAc as the solvent. (*L*)Tyr(OtBu)-NCA was formed using all the tertiary amines, but the conversion rate in most cases was low, and side products were formed. K₂CO₃ caused almost no conversion to occur. Pyridine was the most effective base, giving the highest conversion rate, the cleanest crude product, and the best NCA yield. These results prompted us to evaluate the role of pyridine as a “catalyst” in more detail. We synthesized (*L*)Tyr(OtBu)-NCA from Boc-(*L*)Tyr(OtBu)-OH in the presence of different amounts of pyridine (0.25–2 eq) using AcOEt as a solvent and a 18 h reaction time. Although formation of the NCA was observed using 0.25 and 0.5 pyridine equivalents, the best conversion and recovery of (*L*)Tyr(OtBu)-NCA was obtained when 1 or 2 equivalents of pyridine were used (Figure 1SI). In addition, it appeared that 1.2 T3P[®] equivalent was the best amount to obtain a clean and total conversion (Figure 2SI).

It has been reported that activation of a carboxylic acid by T3P[®] followed by formation of an amide bond in the presence of a nucleophilic amine does not induce epimerization.²¹ However, we investigated whether epimerization occurred during the synthesis of the NCA derivatives in the presence of pyridine. We reacted Boc-(*L*)Asp(OBzl)-OH **1** (1 eq) and Boc-(*D*)Asp(OBzl)-OH **2** (1 eq) with T3P[®] (1.2 eq) and pyridine (1 eq) in EtOAc at room temperature. The corresponding (*L*) and (*D*)Asp(OBzl)-NCAs **3** and **4** were obtained. They were reacted with (*S*)-1-(4-methoxyphenyl)-ethan-1-amine to give diastereomers **5** and **6** (Scheme 2) that were analyzed

separately by HPLC, and after co-injection of a 1:1 mixture (Figures 1SI and 2SI).

Each compound **5** and **6** produced a single peak, indicating no detectable epimerization of the (*L*) and (*D*)Asp(OBzl)-NCAs. These results were also confirmed by ¹H NMR analysis of diastereomers **5** and **6** (SI).

Scheme 2. Epimerization study of Asp(OBzl)-NCA. Synthesis of diastereomers **5** and **6**.



The optimized experimental conditions were used to prepare a series of NCAs (Table 1). The NCAs included some “difficult-to-prepare” NCAs bearing acid-labile protecting groups [e.g., (*L*)Trp(Boc)-NCA, (*L*)Arg(Pbf)-NCA, (*L*)Cys(Trt)-NCA as well as (*L*)Lys(Boc)-NCA for which no cyclization was observed with the N-Boc group side chain].

Table 1. Synthesis of NCAs

NCA	Yield%*	Mp °C
(<i>L</i>)Trp(Boc)-NCA	80	153-154
(<i>L</i>)Arg(Pbf)-NCA	85	122-123
(<i>L</i>)Val-NCA	78	62-63
(<i>L</i>)Tyr(OtBu)-NCA	90	109-110
(<i>L</i>)Phe-NCA	85	88-89
(<i>L</i>)Asp(OBzl)-NCA	85	123-124
(<i>D</i>)Asp(OBzl)-NCA	80	123-124
(<i>L</i>)Thr(OBzl)-NCA	80	120-121
(<i>L</i>)Gln(Xan)-NCA	78	156-157
(<i>L</i>)Asn(Xan)-NCA	90	145-146
(<i>L</i>)Ala-NCA	75	84-85
(<i>L</i>)Ser(OBzl)-NCA	78	68-69
(<i>L</i>)Glu(OBzl)-NCA	78	110-111
(<i>L</i>)Cys(Trt)-NCA	80	122-123
(<i>L</i>)Lys(Boc)-NCA	85	142-143
(<i>L</i>)Lys(Fmoc)-NCA	88	101-102
(<i>L</i>)Tic-NCA	76	166-167
(<i>L</i>)Leu-NCA	86	67-69
Aib-NCA	76	72-73
N-Me-(<i>L</i>)Ala-NCA	71	131-132
N-Benzyl-Gly-NCA	76	152-153
Isatoic anhydride	65	242-243

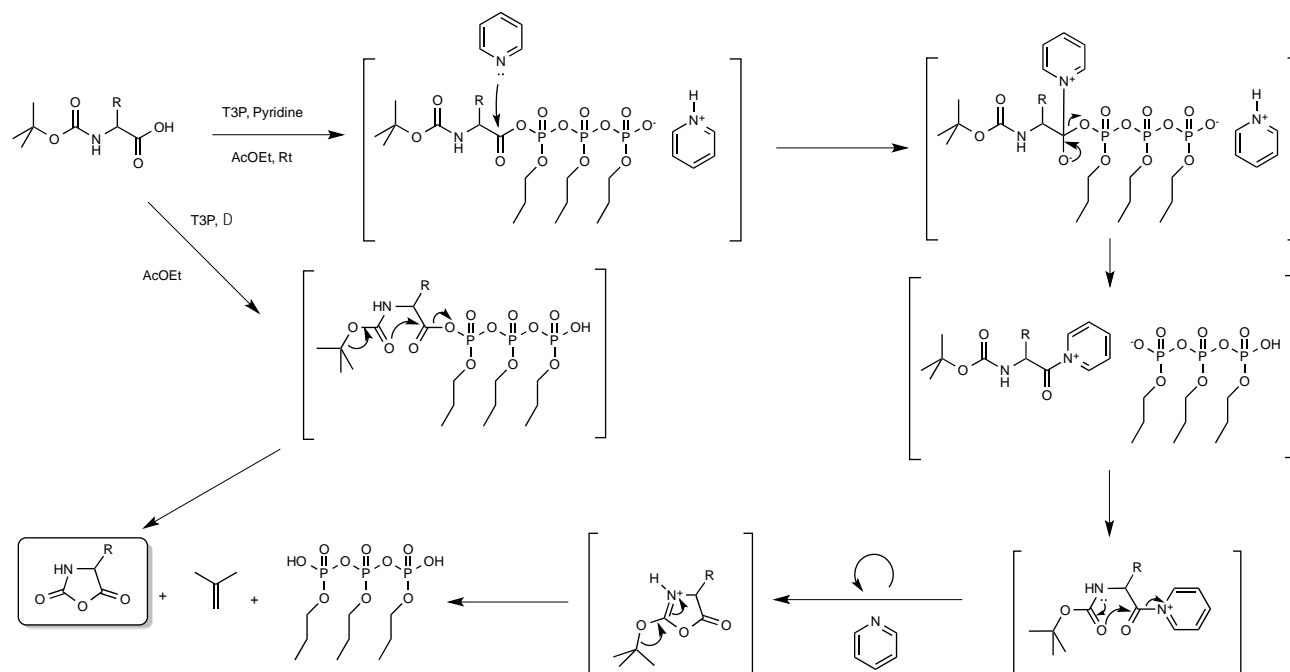
NCAs reported in this Table were prepared under the following experimental conditions: Boc-amino acid derivative (1 eq), T3P[®] (1.2 eq), pyridine (1 eq) in EtOAc at r.t. for 2 h. *Crystalline pure compounds.

We also found that the method could be used to prepare the α -disubstituted amino acid NCA, i.e., Aib-NCA, N-substituted α -amino acid NCAs including N-methyl-(*L*)Ala-NCA, and N-benzyl-Gly-NCA, as well as isatoic anhydride (Table 1). All the NCAs were synthesized at around the gram scale, and were obtained in good yields and at excellent purities after simple precipitation and recrystallization. The detailed physicochemical properties of the NCAs are reported in the Supporting Information.

We found that the Boc protecting group and T3P[®] were both necessary for the cyclization reaction. In fact, no conversion occurred when *Z*-(*L*)Phe-OH or Fmoc-(*L*)Phe-OH was used as the starting material and T3P[®] (1.2 eq) was used, at either

50°C or using 1 eq pyridine. Neither of these phenylalanine N-protected amino acids produced NCA derivatives. In another set of experiments, Boc-(*L*)Phe-OH was reacted with various carboxylic acid activating reagents instead of T3P[®]. These activating reagents were *N,N'*-dicyclohexylcarbodiimide (2 eq), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (2 eq),²⁵ and ((1*H*-benzo[*d*][1,2,3]triazol-1-yl)oxy)tris(dimethylamino)phosphonium hexafluorophosphate (2 eq).²⁶ The experiments with the carboxylic acid activating reagents were performed using the same experimental conditions as those used for the experiments with T3P[®]. Either a faint trace or no (*L*)Phe-NCA was detected by HPLC.

Scheme 3. Mechanism of NCAs formation



The results led to our proposal of the mechanism shown in Scheme 3 for the reaction. To determine whether the method could be scaled up, it was used to prepare (*L*)Leu-NCA from Boc-(*L*)Leu-OH (10 g), (*L*)Lys(Boc)-NCA from Boc-(*L*)Lys(Boc)-OH (10 g), (*L*)Phe-NCA from Boc-(*L*)Phe-OH (20 g), (*L*)Glu(OBzl)-NCA from Boc-(*L*)Glu(OBzl)-OH (25 g), and (*L*)Ala-NCA from Boc-(*L*)Ala-OH (50 g). All these NCAs were obtained at good purities and in good yields [83%, 83%, 83%, 80%, and 77% for (*L*)Leu-NCA, (*L*)Lys(Boc)-NCA, (*L*)Phe-NCA, (*L*)Glu(OBzl)-NCA, and (*L*)Ala-NCA, respectively] after simple workup and simple recrystallization (see SI).

In conclusion, we have developed a mild, non-acidic process for synthesizing α -amino acid NCAs from N-Boc-protected α -amino acid derivatives using T3P[®] as an activating reagent. The process is safe and easy to perform and does not require any specialist equipment. The process generates non-toxic, easy-to-remove by-products and allows a wide range of NCAs to be synthesized with good yields and high puri-

ties. The process is chemically compatible with many amino acid protecting groups that are commonly used in peptide syntheses. The method extends the range of NCA building blocks that can be used to synthesize active pharmaceutical ingredients and peptide-based therapeutic polymers. The yield does not decrease when the process is scaled up, and is easy to perform using simple benchtop equipment. The final product can be recovered easily at an excellent level of purity. The process could be used to prepare NCAs on-demand and on-site in small or large quantities using safe and simple experimental conditions.

General procedure for the preparation of α -Amino Acid N-Carboxyanhydrides (NCAs)

To the Boc-AA-OH (1 eq) dissolved in AcOEt (50 ml) was added pyridine (1 eq), then T3P[®]/AcOEt 50% (1.2 eq) was added dropwise. The mixture was stirred at room temperature for 2 h. The reaction was monitored by LC/MS. The

mixture was then diluted in AcOEt and washed twice with cold water and then with a saturated NaCl solution. The organic layer was dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure, and the crude product crystallized. α -Amino acid N-carboxyanhydride derivatives were obtained through simple recrystallization and were not purified further. The analytical results and physical properties of the products are shown in Table 1 and Supporting Information.

Alternatively, the reaction could be performed without pyridine but at 50 °C, keeping the other conditions the same.

REFERENCES

- (1) Bouifraden, S.; Drouot, C.; El Hadrami, M.; Guenoun, F.; Lecointe, L.; Mai, N.; Paris, M.; Pothion, C.; Sadoune, M.; Sauvagnat, B.; Amblard, M.; Aubagnac, J.-L.; Calmes, M.; Chevallet, P.; Daunis, J.; Enjalbal, C.; Fehrentz, J.-A.; Lamaty, F.; Lavergne, J.-P.; Lazaro, R.; Rolland, V.; Roumestant, M.-L.; Viallefont, Ph.; Vidal, Y.; Martinez, J. Some of the Amino Acid Chemistry Going on in The Laboratory of Amino Acids, Peptides and Proteins. *Amino Acids*, 1999, 16, 345-379.
- (2) Kricheldorf, H. R. *α -Aminoacid-N-Carboxy-Anhydrides and Related Heterocycles: Syntheses, Properties, Peptide Synthesis, Polymerization*; Springer-Verlag, Berlin Heidelberg, 1987, 1-209.
- (3) (a) Hadjichristidis, N.; Iatrou, H.; Pitsikalis, M.; Sakellariou, G. Synthesis of Well-Defined Polypeptide-Based Materials via the Ring-Opening Polymerization of α -Amino Acid N-Carboxyanhydrides. *Chem. Rev.* 2009, 109, 5528-5578. (b) González-Henríquez, C. M.; Sarabia-Vallejos, M. A.; Rodríguez-Hernández, J. Strategies to Fabricate Polypeptide-Based Structures via Ring-Opening Polymerization of N-Carboxyanhydrides. *Polymer*, 2017, 9, 515-613. (c) Deming, T. J. Synthesis of Side-Chain Modified Polypeptides. *Chem. Rev.* 2016, 116, 786-808.
- (4) Duro-Castano, A.; Conejos-Sánchez I.; Vicent, M. J. Peptide-Based Polymer Therapeutics. *Polymer*, 2014, 6, 515-551.
- (5) Nitta S. K.; Numata, K. Biopolymer-based nanoparticles for drug/gene delivery and tissue engineering. *Int. J. Mol. Sci.*, 2013, 14, 1629-1654.
- (6) Bell, C.; Anderson, J.; Ganguly, T.; Prescott, J.; Capila, I.; Lansing, J. C.; Sachleben, R.; Iyer, M.; Fier, I.; Roach, J.; Storey, K.; Miller, P.; Hall, S.; Kantor, D.; Greenberg, B. M.; Nair, K.; Glajch, J. Development of Glatopa® (Glatiramer Acetate): The First FDA-Approved Generic Disease-Modifying Therapy for Relapsing Forms of Multiple Sclerosis. *J. Pharm. Pract.* 2018, 31, 481-488.
- (7) Robin, Y. α -Amino Acid N-Carboxy Anhydrides in Pharmaceutical Innovations: Try Them to Capture New Value. *Chem. Today*, 2015, 33, 26-31.
- (8) Hamaguchi, T.; Matsumura, Y.; Suzuki, M.; Shimizu, K.; Goda, R.; Nakamura, I.; Nakatomi, I.; Yokoyama, M.; Kataoka, K.; Kakizoe, NK105, a Paclitaxel-Incorporating Micellar Nanoparticle Formulation, Can Extend in Vivo Antitumor Activity and Reduce the Neurotoxicity of Paclitaxel. *Br. J. Cancer*, 2005, 92, 1240-1246.
- (9) Park, S.-B.; Sung, M.-H.; Uyama H.; Han D. K. Poly(glutamic acid): Production, composites, and medical applications of the next-generation biopolymer. *Progress Polym. Sci.* 2021, 113, Article 101341.
- (10) Johnson, R. P.; John, J. V.; Kim, I. Recent developments in polymer-block-polypeptide and protein-polymer bioconjugate hybrid materials. *Eur. Polym. J.* 2013, 49, 2925-2948.
- (11) (a) Baars, S.; Drauz, K.-H.; Krimmer, H.-P.; Roberts, S. M.; Sander, J.; Skidmore, J.; Zanardi, G. Development of the Juliá-Colonna Asymmetric Epoxidation Reaction: Part I. Preparation and Activation of the Polyleucine Catalyst. *Org. Process Res. Dev.* 2003, 7, 509-513. (b) Gerlach, A.; Geller, T. Scale-Up Studies for the Asymmetric Julia-Colonna Epoxidation Reaction. *Adv. Synth. Catal.* 2004, 346, 1247-1249.
- (12) Declerck, V.; Nun, P.; Martinez, J.; Lamaty, F. Solvent-Free Synthesis of Peptides. *Angew. Chem. Int. Ed.* 2009, 48, 9318-9321.
- (13) (a) Leuchs, H. Ueber Die Glycin-Carbonsäure. *Ber. Dtsch. Chem. Ges.* 1906, 39, 857-861. (b) Leuchs, H.; Manasse, W. Über die Isomerie der Carbathoxyl-glycyl glycinester. *Ber. Dtsch. Chem. Ges.* 1907, 40, 3235-3249. (c) Leuchs, H.; Geiger, W. Über die Anhydride von α -Amino-N-carbonsäuren und die von α -aminosäuren. *Ber. Dtsch. Chem. Ges.* 1908, 41, 1721-1726.
- (14) (a) Fuchs, F. Über N-Carbonsäure-Anhydride. *Ber. Dtsch. Chem. Ges.* 1922, 55, 2943-2943. (b) Farthing, A. C. Synthetic Polypeptides. Part I. Synthesis of Oxazolidin-2: 5-Diones and a New Reaction of Glycine. *J. Chem. Soc.* 1950, 3213-3217.
- (15) (a) Wilder, R.; Mobashery, S. The Use of Triphosgene in Preparation of N-Carboxy- α -Amino Acid Anhydrides. *J. Org. Chem.* 1992, 57, 2755-2756. (b) Katakai, R.; Iizuka, Y. An Improved Rapid Method for the Synthesis of N-Carboxy α -Amino Acid Anhydrides Using Trichloromethyl Chloroformate. *Org. Chem.* 1985, 50, 715-716.
- (16) Otake, Y.; Nakamura, H.; Fuse, S. Rapid and Mild Synthesis of Amino Acid N-Carboxy Anhydrides: Basic-to-Acidic Flash Switching in a Microflow Reactor. *Angew. Chem. Int. Ed.* 2018, 57, 11389-11393.
- (17) (a) Collet, H.; Bied, C.; Mion, L.; Taillades, J.; Commeyras, A. A New Simple and Quantitative Synthesis of α -Aminoacid-N-Carboxyanhydrides (Oxazolidines-2,5-Dione). *Tetrahedron Lett.* 1996, 9043-9046. (b) Mobashery, S.; Johnston, M. A. New approach to the preparation of N-carboxy α -amino acid anhydrides. *J. Org. Chem.*, 1985, 50, 2200-2202.
- (18) Kudo, H.; Nagai, A.; Ishikawa, J.; Endo, T. Synthesis and Self-Polyaddition of Optically Active Monomers Derived from Tyrosine. *Macromolecules*. 2001, 34, 5355-5357.
- (19) (a) Fujita, Y.; Koga, K.; Kim, H.-K.; Wang, X.-S.; Sudo, A.; Nishida, H.; Endo, T. Phosgene-Free Synthesis of N-Carboxyanhydrides of α -Amino Acids Based on Bisarylcyanates as Starting Compounds. *J. Polymer Sci. Part A: Polymer Chem.* 2007, 45, 5365-5370. (b) Koga, K.; Sudo, A.; Endo, T. Revolutionary Phosgene-Free Synthesis of α -Amino Acid N-Carboxyanhydrides Using Diphenyl Carbonate Based on Activation of α -Amino Acids by Converting into Imidazolium Salts. *J. Polym. Sci. Pol. Chem.* 2010, 48, 4351-4355.
- (20) Enomoto, H.; Nottelet, B.; Halifa, S. A.; Enjalbal, C.; Dupré, M.; Tailhades, J.; Coudane, J.; Subra, G.; Martinez, J.; Amblard, M. Synthesis of Peptide-Grafted Comb Polypeptides via polymerisation of NCA-Peptides. *ChemComm.* 2013, 49, 409-411.
- (21) Dunetz, J. R.; Xiang, Y.; Baldwin, A.; Ringling, J. General and Scalable Amide Bond Formation with Epimerization-Prone Substrates Using T3P® and Pyridine. *Org. Lett.* 2011, 13, 5048-5051.
- (22) (a) Vishwanatha, T. M.; Panguluri, N. R.; Sureshbabu, V. V. Propanephosphonic Acid Anhydride (T3P®) - A Benign Reagent for Diverse Applications Inclusive of Large-Scale Synthesis. *Synthesis.* 2013, 45, 1569-1601. (b) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. Large-Scale Applications of Amide Coupling Reagents for the Synthesis of Pharmaceuticals. *Org. Process Res. Dev.* 2016, 20, 140-177.
- (23) Laconde, G.; Amblard, M.; Martinez, J. A Simple and Versatile Method to Synthesize N-Acyl-Benzotriazoles. *Tetrahedron Lett.* 2019, 341-343.
- (24) Laconde, G.; Amblard, M.; Martinez, J. Unexpected Reactivity of N-Acyl-Benzotriazoles with Aromatic Amines in Acidic Medium (ABAA Reaction). *Eur. J. Org. Chem.* 2019, 1, 85-90.
- (25) Carpino L. A. 1-Hydroxy-7-azabenzotriazole. An Efficient Peptide Coupling Additive. *J. Am. Chem. Soc.* 1993, 115, 4397-4398.
- (26) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. Réactifs de couplage peptidique I (1)-l-hexafluorophosphate de benzotriazolyl N-oxytrisdiméthylamino phosphonium (B.O.P.). *Tetrahedron Lett.* 1975, 1219-122.