ORGANIC LETTERS

2000
Vol. 2, No. 13
1943−1946

Synthesis of Optically Active β-Amino Acid *N*-Carboxyanhydrides

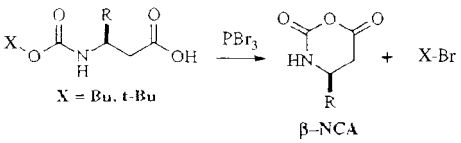
Jianjun Cheng,[†] Joseph W. Ziller,[‡] and Timothy J. Deming*[,†]

Departments of Materials and Chemistry, University of California, Santa Barbara, Santa Barbara, California 93106, and Department of Chemistry, University of California, Irvine, California 92697

tdeming@mrl.ucsb.edu

Received May 5, 2000

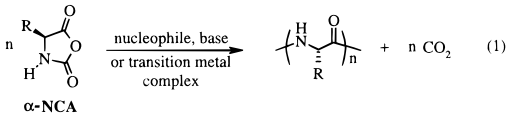
ABSTRACT



Methodology has been developed for the general synthesis of optically active β-amino acid *N*-carboxyanhydrides (β-NCAs) through cyclization of $N_β$-Boc or $N_β$-Cbz β-amino acids using phosphorus tribromide. The formation of β-NCAs was confirmed by spectroscopy as well as an X-ray structural determination of β-homoalanine-*N*-carboxyanhydride. The β-NCA molecules could be polymerized in good yield to give optically active poly(β-peptides) that adopt stable chiral conformations in solution. For example, helical oligo(L-β-homophenylalanine) was synthesized by polymerization of L-β-homophenylalanine-*N*-carboxyanhydride.

The synthesis and characterization of oligomers of β-amino acids, so-called β-peptides, has received considerable interest in recent years.[1−3] β-Peptides differ from their α-peptide analogues by possessing additional conformational freedom due to an extra backbone α-methylene group. Despite this, β-peptide chains containing as few as six monomer repeats can adopt very stable secondary structures in solution, while α-peptide chains of similar length typically do not.[2] Although efficient synthetic methods for preparation of short β-peptides (<20 residues) have become well-established, methods for preparation of poly(β-peptides) are scarce and limited to specific cases. We sought to develop a general methodology for synthesis of optically active poly(β-peptides) using β-amino acid *N*-carboxyanhydride monomers (β-NCAs). Polymers of β-peptides have considerable potential for biomedical applications including drug delivery and therapeutics.[1e,2f] Here we report the high-yield synthesis of optically active β-NCA molecules, derived from $N_α$-urethane-protected β-amino acids, which can in turn be used to prepare poly(β-peptides) that adopt stable secondary structures.

The chemical synthesis of high-molecular-weight poly(α-peptides) is most readily accomplished by the ring-opening polymerization of α-amino acid *N*-carboxyanhydride (α-NCA) monomers (eq 1).[4] However, NCA ring-opening



polymerization has not been well explored for the synthesis of high-molecular-weight poly(β-peptides) primarily since no general method for efficient synthesis of optically pure β-NCAs from amino acids has been developed. α-NCAs are

[†] University of California, Santa Barbara.
[‡] University of California, Irvine.

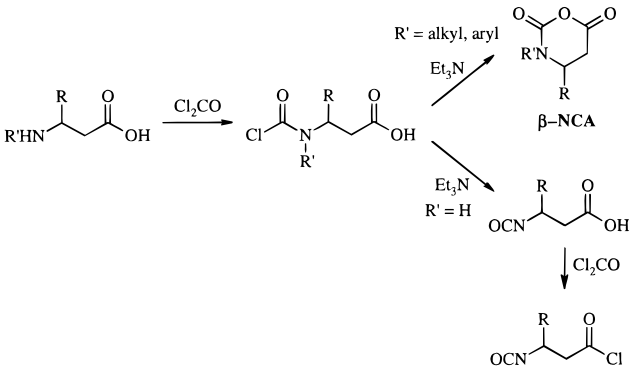
(1) (a) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071−13072. (b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387*, 381. (c) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (d) Appella, D. H.; Barchi Jr; J. J.; Durell, S. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 2309−2310. (e) Porter, E. A.; Wang, X.; Lee, H.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.

(2) (a) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913−941. (b) Seebach, D.; Ciceri, P. E.; Overhand, M.; Jaun, B.; Rigo, D.; Oberer, L.; Hommel, U.; Amstutz, R.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 2043−2067. (c) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015−2022. (d) Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2141−2156. (e) Seebach, D.; Abele, S.; Sifferlen, T.; Hänggi, M.; Gruner, S.; Seiler, P. *Helv. Chim. Acta* **1998**, *81*, 2218−2243. (f) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1223−1226.

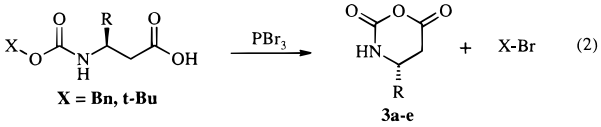
10.1021/ol000122w CCC: $19.00
Published on Web 06/03/2000

readily synthesized either by phosgenation of free α-amino acids (Fuchs−Farthing method) or through the cyclization of N_α-urethane-protected α-amino acids (Leuchs method).[4] These methods are not universally applicable for the synthesis of β-NCAs since the kinetics of ring closure and the thermodynamic stability of NCAs decreases as ring size increases from 5 (α-NCAs) to 6 (β-NCAs).[4] For instance, when β-amino acids are treated with phosgene, the major isolated products are uncyclized *N*-chloroformyl β-amino acids rather than the desired β-NCAs (Scheme 1).[5] Treatment

Scheme 1. Reactions of β-Amino Acids with Phosgene



of these compounds with base (e.g., Et_3N) generally results in low yields of β-NCAs unless they are N-substituted. The poor yields are due to isocyanate formation, which competes with the ring closure.[5] The Fuchs−Farthing method is thus not very useful for β-NCA synthesis since it is the N-unsubstituted derivatives that are desired due to their ability to form H-bonded secondary structures. The formation of N-unsubstitued β-NCAs is best accomplished using the Leuchs method of NCA synthesis, specifically cyclization of N_β-Boc and N_β-Cbz β-amino acids using PBr_3 (eq 2).[6]



(2)

All previous β-NCA preparations using the Leuchs method were limited to synthesis of racemic NCAs, primarily since only racemic β-amino acids were readily available.[5b,6] The random stereocopolymers derived from polymerization of these monomers were not particularly useful since their irregularity prevents the adoption of stable secondary structures. In fact, the number of optically active poly(β-peptides) that have been reported is quite small. Most of these examples contain a limited set of side-chain functionalities, which were derived from a small pool of readily available precursors. However, these polymers were not synthesized from β-NCAs but were prepared using either the ring-opening polymerization of β-lactams[7] or polycondensation of carboxyl-activated α-alkyl-L-aspartates.[8] We sought to develop methods for the general preparation of optically pure poly(β-peptides) utilizing recently developed chemistry that provides a wide variety of optically pure β-amino acids. These β-amino acid starting materials (**2a**−**k**) were synthesized according to the methods developed by Seebach,[2] namely, the Arndt−Eistert homologation of N_α-protected α-amino acids (**1a**−**k**) to the intermediate diazo ketones, followed by Wolff rearrangement of the diazo ketones to give the desired products (**2a**−**k**) in good yield (60−90% overall, Scheme 2). The only exception was the conversion of **1e** to **2e**, which could only be obtained in 15% overall yield.

Following literature precedent,[6] PBr_3 was used to cyclize the acids, **2a**−**k**, into the corresponding β-NCAs, **3a**−**f** (eq 2). The β-NCA structure was confirmed by the X-ray structural determination of **3a**.[9] With stoichiometric PBr_3 (0.34 equiv), consumption of the starting material was found to be slow and the reactions did not go to completion. Use of 0.6 equiv of PBr_3 was found to be optimal for giving both high conversion and minimal side reactions (i.e., amine deprotection by liberated acid) (Table 1). Reactions in

Table 1. Synthesis of β-NCAs (**3a**−**f**) from Urethane-Protected β-Amino Acid Precursors (**2a**−**k**). Yields Are for Purified, Isolated Products

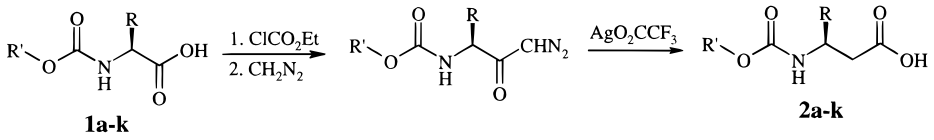
entry	substrate	[substrate] (M)	product β-NCA	yield (%)
1	**2a**	0.5	**3a**	43
2	**2a**	0.5	**3a**	47[a]
3	**2a**	0.1	**3a**	95
4	**2b**	0.1	**3b**	80
5	**2c**	0.1	**3c**	85
6	**2d**	0.1	**3d**	75
7	**2e**	0.1	**3e**	54
8	**2f**	0.1	**3f**	45
9	**2f**	0.1	**3f**	58[a]
10	**2g**	0.1	**3a**	93
11	**2h**	0.1	**3b**	88
12	**2i**	0.1	**3c**	74
13	**2j**	0.1	**3d**	70
14	**2k**	0.1	**3e**	52
15	**2k**	0.1	**3e**	64[a]

[a] Triethylamine (1 equiv) was added to these reactions.

different solvents (toluene, dioxane, THF, and CH_2Cl_2) revealed that CH_2Cl_2 consistently gave the highest yields of

(3) Gung, B. W.; Zou, D.; Stalcup, A. M.; Cottrell, C. E. *J. Org. Chem.* **1999**, *64*, 2176−2177.
(4) Kricheldorf, H. *α-Aminoacid-N-Carboxyanhydrides and Related Heterocycles*; Springer-Verlag: 1987; pp 11−16.
(5) (a) Birkofer, L.; Modic, R. *Liebigs Ann. Chem.* **1957**, *604*, 56. (b) Zilkha, A.; Burstein, Y. *Biopolymers* **1964**, *2*, 147−161.
(6) Birkofer, L.; Modic, R. *Liebigs Ann. Chem.* **1959**, *628*, 162−172.
(7) (a) Graf, R.; Lohaus, G.; Börner, K.; Schmidt, E.; Bestian, H. *Angew. Chem.* **1962**, *74*. 523. (b) Bestian, H. *Angew. Chem.* **1968**, *80*, 304. (c) Schmidt, E. *Angew. Makromol. Chem.* **1970**, *14*, 185−202 (d) Chen, F.; Lopero, G.; Goodman, M. *Macromolecules.* **1974**, *7*, 779−783. (e) García-Alvarez, M.; Martínez De Ilarduya, A.; López-Carrasquero, F.; Fernández-Santín, J. M.; Muñoz-Guerra, S. *J. Polym. Sci. Polym. Chem.* **1996**, *34*, 1959−1968. (f) Ilarduya, A. M.; Alaman, C.; Garcia-Alvarez, M.; López-Carrasquero, F.; Muñoz-Guerra, S. *Macromolecules*, **1999**, *32*, 3257−3263.

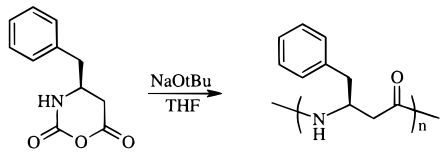
Scheme 2. Synthesis of Optically Active β-Amino Acids from α-Amino Acids



Entry	R'	R
a	Bn	CH_3
b	Bn	$CH(CH_3)_2$
c	Bn	$CH_2CH(CH_3)_2$
d	Bn	$CH_2C_6H_5$
e	Bn	$CH_2CH_2C(O)OCH_2C_6H_5$
f	Bn	$CH_2CH_2CH_2CH_2NHC(O)OCH_2C_6H_5$
g	*t*-Bu	CH_3
h	*t*-Bu	$CH(CH_3)_2$
i	*t*-Bu	$CH_2CH(CH_3)_2$
j	*t*-Bu	$CH_2C_6H_5$
k	*t*-Bu	$CH_2CH_2C(O)OCH_2C_6H_5$

β-NCAs. It was also found that yields were greatest when the reactions were conducted at lower substrate concentrations (<0.1 M) and in the presence of a base (e.g., triethylamine) (Table 1). These optimized methods have been used to synthesize a variety of β-NCAs and appear to be generally applicable. Larger β-amino acid side chains, however, were observed to have an adverse effect on β-NCA formation. With other parameters held constant, the yields of β-NCAs decreased as side chain size increased (entries 3−8, Table 1). This effect was likely due to a decreased rate of cyclization caused by the steric hindrance of the substituents. When N_β-*t*-Boc β-amino acids **2g**−**k** were used to make β-NCAs, the yields were roughly same as those synthesized from N_β-Cbz β-amino acids **2a**−**f**. Other bromination reagents such as oxalyl bromide (1.0 equiv) were also found to be effective for β-NCA synthesis under similar conditions. Optical purities of the β-NCAs were determined by reaction with L-alanine to form dipeptides,[10] followed by HPLC analysis of the diastereomeric product(s).[9] In general, the β-NCAs were found to be > 98% enantiomerically pure.

To illustrate the utility of β-NCAs for synthesis of optically active poly(β-peptides), oligomers of L-β-homophenylalanine (oligo(β-HPhe)) were synthesized from L-HPhe β-NCA using NaO*t*Bu initiator in THF (eq 3). The oligo(β-HPhe) was



(3)

found to precipitate from the reaction mixture during the polymerization, which served to limit the molecular weight (oligomers ranged from tetramers to pentadecamers).[9] This product was characterized using FTIR, ^{1}H NMR, MALDI-(TOF)-MS, and circular dichroism (CD) to confirm its identity as an oligo(β-peptide) and analyze its conformation. FTIR analysis showed Amide I and Amide II bands at 1638 and 1552 cm^{-1}, respectively, that were indicative of the formation of peptide linkages. These absorptions were similar to those found by Goodman for poly(L-β-homoalanine) prepared using a different method.[7d] Oligo(β-HPhe) was found to be insoluble in most organic solvents, but it was soluble in hexafluoro-2-propanol (HFIP) and trifluoroacetic acid. The CD spectrum of this oligomer in HFIP possessed a minimum at 218 nm and a maximum at 202 nm with molar ellipticities of -2.98×10^4 and 3.49×10^4 deg cm^2/mol, respectively (Figure 1). These spectral features are very

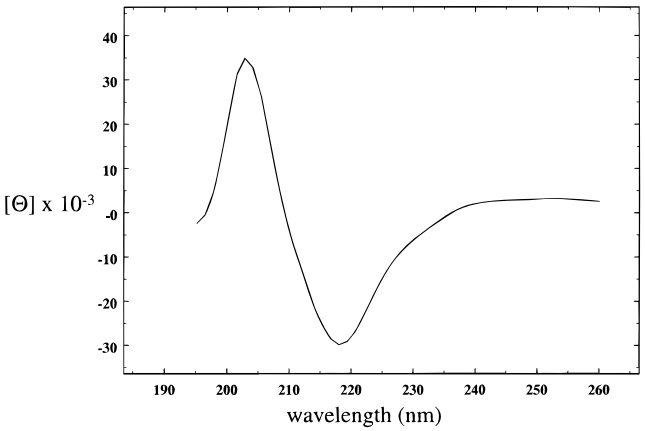


Figure 1. CD spectrum of oligo(β-HPhe) (M_n = 1370) in HFIP ([oligo(β-HPhe)] = 0.5 mg/mL).

similar to those described by Seebach for the heptamer of L-β-homolysine, which was reported to adopt a 3_1 helical

(8) (a) Fernández-Santin, J. M.; Aymami, J.; Rodríguez-Galán, A.; Muñoz-Guerra, S.; Subirana, J. A. *Nature (London)* **1984**, *311*, 53−54. (b) Fernández-Santin, J. M.; Muñoz-Guerra, S.; Rodríguez-Galán, A.; Aymami, J.; Lloveras; J.; Subirana, J. A.; Giralt, E.; Ptak, M. *Macromolecules* **1987**, *20*, 62−68.

conformation.[2] This result indicates that β-NCAs are useful precursors to poly(β-peptides) that can adopt stable chiral secondary structures. Polymerization of other β-NCAs and structural analysis of the resulting poly(β-peptides) are currently being pursued.

Acknowledgment. This work was supported by National Science Foundation CAREER Award No. CHE-9701969 and a grant from the University of California Biotechnology Training Program and partially supported by the MRSEC program of the National Science Foundation under Award No. DMR-9632716. T.J.D. is grateful for Alfred P. Sloan and Beckman Young Investigator Fellowships.

Supporting Information Available: Details of all reactions and polymerizations and X-ray crystal structure of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000122W

(9) See the Supporting Information.

(10) Hirschmann, R.; Strachan, R. G.; Schwam, H.; Schoenewaldt, E. F.; Joshua, H.; Barkemeyer, B.; Veber, D. F.; Paleveda, W. J., Jr.; Jacob, T. A.; Beesley, T. E.; Denkewalter, R. G. *J. Org. Chem.* **1967**, *32*, 3415−3425.