Tetrahedron Letters,Vol.29,No.46,pp 5859-5862,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

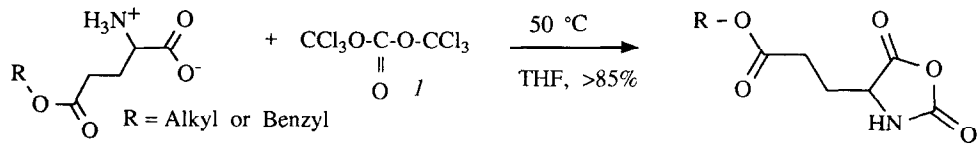
THE PREPARATION OF N-CARBOXYANHYDRIDES OF α-AMINO ACIDS USING BIS(TRICHLOROMETHYL)CARBONATE

William H. Daly and Drew Poche'*
Contribution from the Macromolecular Studies Group,
Department of Chemistry, Louisiana State University
Baton Rouge, Louisiana 70803 U.S.A.

Abstract: A synthesis of the N-carboxyanhydrides (NCA's) of several α-amino acids using bis(trichloromethyl)carbonate, *1*, is reported. The triphosgene is used to supply phosgene *in situ* in stoichiometric amounts; it is particularly effective for preparing NCA's of amino acids with long, aliphatic side chains.

In the many decades since Leuchs[1] first reported the preparation of the NCA derivatives of amino acids, numerous procedures[2-7] have been reported for the synthesis of these important cyclic monomers. Since NCA's are used primarily as monomers for high molecular weight polypeptide preparations, a clean synthesis is required to assure production of polymerization grade material. Direct addition of phosgene to the α-amino acid has been the preferred route, principally because facile, rapid reaction prevents racemization of the resulting NCA[8]. A method developed by Goodman et.al.[9] employs a benzene solution of phosgene which circumvents the need for large excesses of the gas. Indiscriminate addition of phosgene can lead to side reactions, the products of which can inhibit subsequent polymerization of the NCA[10]. Further, it is hard to meter the highly toxic gas and maintain the proper stoichiometric balance. Since we prepare NCA's on a routine basis in our laboratory, we were interested in a phosgene substitute which was easier to handle and would give comparable yields in reasonable reaction times. Trichloromethyl chloroformate (diphosgene) has been evaluated as such a substitute[11], but it is necessary to catalyze the dissociation process with carbon black to obtain efficient cyclization[12]. A recent paper by Eckert and Forster [13] outlined the synthesis and general utility of triphosgene as a phosgene substitute. Thus, we were encouraged to apply it to the preparation of NCA's.

Triphosgene, *1*, prepared by exhaustive chlorination of dimethyl carbonate, has proven in our hands, to be generally useful for the synthesis of α-amino acid NCA's. It is a crystalline solid which can be safely handled and stored; no catalyst is required to deliver three equivalents of phosgene *in situ*. Small scale preparations are simplified because exact amounts of *1* can be weighed and added quantitatively. Because *1* is soluble in the typical recrystallization solvents for NCA's, tetrahydrofuran (THF) and hexane, removal of any residual triphosgene from the NCA is accomplished by recrystallization of the product.



Treatment of an amino acid suspension in anhydrous THF with 1/3 eq. of *I* at 40-50°C usually leads to a completely homogeneous solution of the corresponding NCA within 1-3 hours. Typically the reaction is performed by suspending 10 g of amino acid in 100 mL of THF, warming the mixture to 50°C, and then adding an equivalent of *I*. If a clear solution has not formed within 1 hr, 2-3 aliquots(0.05 eq) of *I* may be added at 30 min intervals. After three hours the reaction mixture was poured into 300 mL of hexane, and the resulting suspension stored at -20°C overnight to assure complete crystallization. The NCA was recrystallized from THF/hexane to a constant melting point; the NCA of γ-stearyl-L-glutamate can be recrystallized from hexane using 15 mL of solvent/g of product. Compiled in Table I are the α-amino acids surveyed, the reaction times employed, and isolated yields. The low yields obtained from alanine, valine, and leucine can be attributed to their failure to dissolve completely. Amino acids with long sidechain groups, namely 2-aminostearic acid and γ-stearyl-L-glutamate,[14] dissolve within 1 hour. L-Phenylalanine, O-benzyl-L-tyrosine,[15] and γ-benzyl-L-glutamate require longer reaction times but complete dissolution does occur. Table I also shows that 1 equivalent of phosgene (1/3 of an equivalent of triphosgene) suffices.

Table I. Reaction of *I* with Amino Acids in THF

Amino Acid (AA)	*I*/3 : AA	% yield [a]	mp °C [b]	Scale, g.	Dissolution time, hr	$[\alpha]_D$
γ-stearyl-L-glutamate	1.04	89.5	77-78	10.0	<1	-18.10 [e]
DL-2-aminostearic acid	1.07	81.8	98-99	0.3	1	---
γ-benzyl-L-glutamate	1.17	85.8	96-97	0.4	<3	-19.11
O-benzyl-L-tyrosine	1.20	89.4	142	0.4	3 [c]	-88.45
L-phenylalanine	1.13	83.0	91-92	5.0	3	-108.30
L-leucine	1.16	66.8	78-79	2.5	d	-37.40
L-alanine	1.26	58.5	91-92	5.0	d	---
DL-valine	1.11	82.7	80-81	5.0	d	---

a isolated yield
b uncorrected melting points, Fischer-Johns hot stage
c slight suspension remained
d insoluble material removed by filtration after about 4 h.
e filtered chloroform solution; approximate concentration 1.0 g/dl

Triphosgene undergoes nucleophilic attack at the carbonyl carbon; the trichloromethoxy (Cl_3CO-) leaving group dissociates to a chloride anion and a molecule of phosgene, which reacts immediately.[13].

Hence, there is no excess phosgene in solution. However as the reaction proceeds, the HCl by-product protonates the unreacted amino function of residual amino acid, reducing its nucleophilicity and solubility. This problem is more acute with amino acids containing short chain alkyl groups, as evidenced by a reduction in isolated yields of NCA's. Periodic sparging with nitrogen improves product yields by driving the HCl evolved from the reaction medium. Addition of excess triphosgene fails to drive the reaction to completion. Reaction times in excess of 5 hours lead to discoloration, which complicates NCA purification.

The optical rotations of the NCA's tabulated in Table I have not been reported to date. Solutions used for polarimetry were prepared immediately prior to measurement and the rotations observed were monitored over a two hour interval to assure that no degradation and/or polymerization was occurring during the measurement.

Table II. Proton NMR Data for NCA's.

NCA	Observed Chemical Shift ($CDCl_3$)
γ-stearyl-L-glutamate	6.62 (s, N-H), 4.40 (t, C-H), 4.09 (t, -OCH $_2$-R), 2.56 (m, γ-CH_2), 2.20 (m, β-CH_2), 1.26 (s, alkyl-CH_2 chain), 0.88 (t, -CH_3)
γ-benzyl-L-glutamate	7.37 (s Ar-H), 6.71 (s, N-H), 5.15 (s, -CH_2-benzylic), 4.39 (t, C-H), 2.61 (m, γ-CH_2), 2.14 (m, β-CH_2)
DL-2-aminostearic acid	6.33 (s, N-H), 4.35 (t, C-H),1.26 (s, alkyl -CH_2 chain), 0.88 (t, -CH_3)
O-benzyl-L-tyrosine	7.39 (m Ar-H, O-benzyl), 7.25-6.89 (m Ar-H, try), 5.91 (s, N-H), 5.04 (s, -CH_2-benzylic), 4.46 (t, N-C-H), 3.30-2.85 (m, β-CH_2)
L-phenylalanine	7.46-7.21 (m Ar-H), 6.47 (s, N-H), 4.55 (m, C-H), 3.36-2.88 (m, -CH_2-benzylic)
L-leucine	7.03 (s, N-H), 4.34 (m, C-H), 1.82 (m, β-CH_2), 0.98 (dd, gem di-CH_3)
L-alanine	6.66 (s, N-H), 4.46 (q, C-H), 1.60 (d, -CH_3)
DL-valine	7.25 (s, N-H), 4.22 (d, N-C-H), 2.28 (m, -CH), 1.06 (m, gem di-CH_3)

Table II summarizes the ^{1}H NMR data. Interestingly, the non-equivalence[16] of the beta protons is clearly discernible in the L-phenylalanine NCA spectrum, giving rise to a series of doublets centered at 3.10 ppm. In a like manner, the O-benzyl-L-tyrosine NCA exhibits this non-equivalence of the benzylic CH_2 adjacent to the α-CH proton. The non-equivalence of the leucine methyl protons appears as two closely spaced doublets centered at 0.98 ppm. No evidence for amino acid racemization could be detected by NMR.

We are interested primarily in the polymers formed from γ-stearyl-L-glutamate; the peptide backbone assumes a relatively rigid α-helical conformation while the long hydrocarbon side chains propagating from each repeating unit impart high solubility in non-polar solvents. Further, the polymers exhibit thermotropic liquid crystalline behavior [17-20]. We have isolated the β-sheet conformation of poly(γ-stearyl-L-glutamate) by fractionation; this material forms gelatinous suspensions in THF and

THF-acetone mixtures. Further details of the polymerization of the NCA's and the properties of the polypeptides with long chain alkyl substituents will be reported in future publications.

Acknowledgements: The authors wish to thank Professor Mark McLaughlin of our department for pointing out the Eckert and Forster paper. IBM Almaden Research Center graciously provided access to the polarimeter.

References and Notes:

1. H. Leuchs, **Chem. Ber.**, *39*, 857 (1906).
2. R. Wakasa, K. Shibata, Y. Takahashi, and S. Ishida, **Japanese Patent** 6901974 (1969); **Chem. Absts.**, *71*, 13373q.
3. F. Fuchs, **Chem. Ber.**, *55*, 2943 (1922).
4. A.C. Farthing, **J. Chem. Soc.**, 3213 (1950).
5. T. Curtius and W. Siber, **Chem. Ber.**, *54*, 1430 (1921).
6. C.H. Bamford and H.J. Block, **J. Chem. Soc.**, 232 (1955).
7. Y. Koiwa, K. Tatsukawa, A. Miike, M. Teranishi and Y. Fujimoto, **J. Synth. Org. Chem., Japan.**, *33*, 628 (1975).
8. Y. Shalitin, "N-Carboxy-α-Amino Acid Anhydrides" in Ring Opening Polymerization, Vol. 2 K.C. Frish and S.L. Reegen, ed., Marcel Dekker, New York, 1969, 421.
9. W.D. Fuller, M.S. Velander, and M. Goodman, **Biopolymers**, *15*, 1869 (1976).
10. H. Block, Poly(γ-Benzyl-L-Glutamate) and Other Glutamic Acid Containing Polymers, Polymer Monographs, Gordon and Breach, New York, 1983, 23.
11. M. Oya, R. Katakai, H. Nakai and Y.Iwakara, **Chem. Lett.**, 1143 (1973).
12. R. Katakai and Y. Iizuka, **J. Org. Chem.**, *50*, 715 (1985)
13. H. Eckert and B. Forster, **Angew. Chem. Int. Ed. Eng.**, *26*, 894 (1987). Triphosgene is available commercially from Aldrich Chemical Company, Inc.
14. D. Wasserman, J.D. Garber and F.M. Meigs, **US Patent** 3,285,953 (1966). Treatment of a mixture of glutamic acid and stearyl alcohol in *tert*-alcohol in the presence of conc. H_2SO_4 for one hour affords the γ-ester uncontaminated by any diester.
15. E. Wunsch, G. Fries and A. Zwick, **Chem. Ber.**, *91*, 542 (1958). Complexing the amino and carboxylate groups of tyrosine allows selective alkylation of the phenoxide function.
16. H. Kricheldorf, α-Amino-N-Carboxyanhydrides and Related Heterocycles, Springer-Verlag, New York, 1987.
17. J. Watanabe, H. Ono, I. Uematsu and A. Abe, **Macromolecules** , *18*, 2141 (1985).
18. J. Watanabe, Y. Fukuda, R. Gehani, H. Ono and I. Uematsu, **Macromolecules**, *17*, 1004 (1984).
19. J. Watanabe, M. Goto and T. Nagase, **Macromolecules**, *20*, 298 (1987).
20. J. Watanabe and T. Nagase, **Polymer J. Japan**, *19*, 781 (1987).

(Received in USA 3 August 1988)