Ethyl (*E*)-3-(Trimethylsilyl)methacrylate (12). To a stirred solution of 131 μL (1.50 mmol) of oxalyl chloride in 8.0 mL of dichloromethane at −78 °C was added 121 μL (1.70 mmol) of dimethyl sulfoxide. After 10 min, a solution of 104 mg (1.00 mmol) of (trimethylsilyl)methanol in 2 mL of dichloromethane was added over 4 min to the reaction mixture. After 15 min, 0.52 mL (3.7 mmol) of triethylamine was added over 1 min. After 5 min at −78 °C, a solution of 690 mg (1.9 mmol) of ethyl 2-(triphenylphosphoranylidene)propionate was added over 3 min. The reaction mixture was then allowed to warm to room temperature, was diluted with 70 mL of ether, and was then washed with 40 mL of water and then 40 mL of saturated aqueous NaCl. The organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 10 g of silica gel with 3:97 ether/petroleum ether afforded 101 mg (54%) of the olefin **12** as a colorless oil: R_f 0.33 (silica gel, 5:95 ether/petroleum ether); IR ($CHCl_3$) 3000, 2960, 1700, 1610, 1370, 1330, 1320, 1210, 1100, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.17 (s, 9 H, $(CH_3)_3Si$), 1.30 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.00 (s, 3 H, CH_3C), 4.17 (q, 2 H, J = 7 Hz, CH_3CH_2), 6.82 (s, 1 H, CH=C); mass spectrum; m/e (relative intensity, composition) 171 (100, $C_8H_{15}O_2Si$), 143 (46, $C_7H_{15}OSi$), 113 (5, $C_6H_{13}Si$), 75 (38, $C_3H_7O_2$), 73 (32, $C_3H_5O_2$, C_3H_9Si).

Registry No. 1, 96150-76-4; **3**, 96150-78-6; **4**, 96056-09-6; *trans*-**6**, 96056-10-9; *cis*-**6**, 96149-11-0; **7**, 1117-86-8; *trans*-**9**, 96245-80-6; *cis*-**9**, 96245-81-7; **10**, 3219-63-4; **12**, 96245-82-8; oxalyl chloride, 79-37-8; methylmagnesium bromide, 75-16-1; methyl (triphenylphosphoranylidene)acetate, 2605-67-6; ethyl 2-(triphenylphosphoranylidene)propionate, 5717-37-3.

A New Approach to the Preparation of *N*-Carboxy α-Amino Acid Anhydrides

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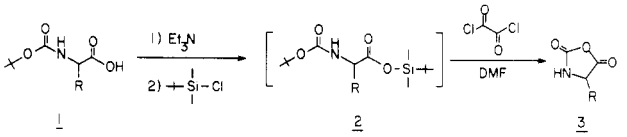
N-Carboxy α-amino acid anhydrides (NCA's) would appear to be reagents of considerable utility in peptide synthesis, since their preparation achieves both amino-group protection and carboxylate activation in a single step. While the NCA's have been used routinely in prepartion of homopolymers of high molecular weight and in random copolymerizations,[1] this strategy has found only limited application in the stepwise synthesis of polypeptides.[2] Dipeptide formation, by condensation of one amino acid with the NCA of a second, is a facile process,[3] but there are difficulties in controlling the amide bond-forming reaction when the NCA technology is applied to heteropolymers.[4] An additional problem is attributable to the fact that the *N*-carboxy anhydrides themselves are accessible by less-than-straightforward routes. These often involve harsh reaction conditions, long reaction times with poor yields and—not inconsequentially—the use of severely toxic reagents.

Scheme I



N-Carboxy anhydrides have been prepared most frequently by treatment of an amino acid with large excesses of phosgene at elevated temperatures,[5] an obviously hazardous method. Goodman and co-workers[6] introduced a technique for monitoring NCA formation by infrared spectroscopy, which allows the use of standardized phosgene solutions. While this approach reduces the quantity of phosgene typically specified in the older literature, the amounts required are by no means stoichiometric. In an attempt to avoid the use of phosgene altogether, Oya and his colleagues[7] have prepared NCA's using trichloromethyl chloroformate, the socalled phosgene dimer. But this method is not wholly satisfactory; the NCA of alanine, for example, is obtained only after extensive workup and then in only about 60% yield. Moreover, trichloromethyl chloroformate is not widely available commercially.

Alternative procedures for preparation of the *N*-carboxy anhydrides include reaction of the N^{α}-protected amino acids with PBr_3.[8] In fact, the NCA's of glutamine and asparagine can be prepared only by treatment with PBr_3; the phosgene methods gives dehydration to the corresponding cyano derivatives.[2b,8] Generally, methods involving the use of the phosphoro halides suffer from the need for very long reaction times, extensive product purification and, frequently, very poor yields.

We have been involved in the preparation of antibacterial peptides,[9] which occasions a general interest in synthetic methods allowing for the facile introduction of β-haloalanyl residues into peptides. In this connection, we have discovered that the *N*-carboxy anhydrides of several α-amino acids (**3**), including β-chloro-L-alanine (Table I), can be formed by reaction of an *N*-*tert*-butoxycarbonyl (BOC) amino acid (**1**) with *tert*-butyldimethylsilyl chloride and subsequent treatment of the resulting silyl ester (**2**) with oxalyl chloride in the presence of dimethylformamide (DMF) (Scheme I). The sequence **1** → **3** is an adaptation of the method for preparation of carboxylic acid chlorides (and esters) developed by Wissner and Grudzinskas.[10]

In a typical reaction, an *N*-BOC amino acid is dissolved in ethyl acetate and is then treated with 1 equiv each of triethylamine and *tert*-butyldimethylsilyl chloride. Ad-

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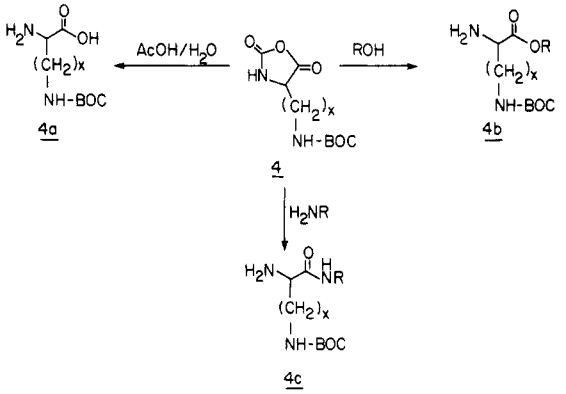
Table I. *N*-Carboxy α-Amino Acid Anhydrides Prepared

anhydride **3**	yield, %	TLC (R_f)[a]	IR,[b] cm^{-1}	mp, °C	anal.	^1H HMR,[c] δ
a, R = CH_3 (L-Ala)	100	0.47 (C)	1850, 1780	88–90	C, H, N	1.49 (d, 3 H, β-H_3, J = 7.0 Hz), 4.56 (q, 1 H, α-H, J = 7.0 Hz)
b, R = CH_2Cl (β-Cl-L-Ala)	100	0.77 (A)	1850, 1733	115–116	C, H, N	4.01 (dd, 1 H, β-H, J = 12.1, 3.0 Hz), 4.07 (dd, 1 H, β-H, J = 12.2, 3.2 Hz), 5.03 (dd, 1 H, α-H, J = 3.0, 3.2 Hz)
c, R = $CH(CH_3)_2$ (L-Val)	100	0.51 (B)	1855, 1784	69–70	C, H, N	0.99 (d, 3 H, γ-H_3, J = 6.4 Hz), 1.07 (d, 3 H, γ-H_3, J = 6.4 Hz), 2.17–2.24 (m, 1 H, β-H); 4.42 (d, 1 H, α-H, J = 3.9 Hz)
d, R = $CH_2C_6H_5$ (L-Phe)	100	0.50 (B)	1855, 1788	119–125[d]	C, H, N	3.14 (dd, 1 H, β-H, J = 14.2, 4.6 Hz), 3.23 (dd, 1 H, β-H, J = 14.3, 4.8 Hz), 4.84 (dd, 1 H, α-H, J = 4.6, 4.9 Hz), 7.27–7.30 (m, 5 H, C_6H_5)
e, R = $CH_2(CO_2)CH_2C_6H_5$ (β-benzyl-L-Asp)	100	0.45 (B)	1857, 1790, 1725	120–121	C, H, N	3.08 (dd, 1 H, β-H, J = 15.3, 2.9 Hz), 3.15 (dd, 1 H, β-H, J = 15.3, 3.6 Hz), 4.80 (t, 1 H, α-H, J = 3.3 Hz), 5.16 (s, 2 H, $CH_2C_6H_5$, 7.33–7.37 (m, 5 H, C_6H_5)
f, R = $CH_2SCH_2C_6H_5$ (S-benzyl-L-Cys)	100	0.54 (B)	1858, 1790	103–104	C, H, N	2.95 (dd, 1 H, β-H, J = 14.6, 5.0 Hz), 3.02 (dd, 1 H, β-H, J = 14.6, 4.0 Hz), 3.80, 3.90 (2 d, 2 H, $CH_2C_6H_5$, J = 14.2 Hz), 4.81 (dd, 1 H, α-H, J = 4.0, 5.0 Hz), 7.24–7.36 (m, 5 H, C_6H_5)
g, R = $(CH_2)_3NH(CO)O$-t-Bu (N^{α}-BOC-L-Orn)	100[e]	0.83 (D)	1855, 1785, 1700	*f*	*g*	1.55 (s, 9 H, t-Bu), 1.60–1.70 (m, 2 H, γ-H_2), 1.70–1.85 (m, 2 H, δ-H_2), 3.63 (t, 2 H, β-H_2, J = 6.7 Hz), 4.55 (t, 1 H, α-H, J = 6.3 Hz)
h, R = $CH_2NH(CO)O$-t-Bu (N^{β}-BOC-D,L-diaminopropionate)	100[e]	0.82 (E)	1855, 1785, 1700	*f*	*g*	1.41 (s, 9 H, t-Bu), 3.57 (m, 2 H, β-H_2), 4.62 (t, 1 H, α-H, J = 4.8 Hz)

[a] Silica gel; letters in parentheses denote eluting solvent system (see text). [b] Film, in $CHCl_3$, carbonyl stretches. [c] 500 MHz; δ in ppm, downfield from tetramethylsilane, in acetone-d_6. [d] Sintered at ~87 °C. [e] Yield estimated by NMR integration. [f] Oil, solid only under reduced pressure. [g] Gives unreliable analytical data because of slight impurities trapped in the oily product (see text for details).

Scheme II



dition of the organosilane immediately gives precipitation of the triethylamine hydrochloride, which is recovered in >98% yield. We do not routinely isolate the silyl ester **2** but merely remove the solvent in vacuo and redissolve the resulting oil in methylene chloride at 0 °C. Oxalyl chloride is then added, followed by 2 or 3 drops of DMF. Evolution of gas (presumably CO_2 and CO)[10] is observed almost immediately upon addition of DMF and ceases within 2 or 3 minutes. The solution is allowed to warm to room temperature and is then evaporated in vacuo. Evaporation of the solvent gives crystalline *N*-carboxy anhydrides.[11] Proton NMR shows that the product crystals contain minute quantities of DMF, which is easily removed by subsequent recrystallization. All of the *N*-carboxy anhydrides of Table I form quantitatively by this method. They can be isolated after no more than 3–4 h of bench-time, including workup and recrystallization.

As in previous methods for preparation of the NCA's, the sequence **1** → **3** most likely involves a key cyclization of an intermediate α-amino acid chloride, formed upon addition of oxalyl chloride to the silyl ester **2**. An obvious advantage of this route over others is the ability to form the reactive acid chloride under very mild reaction conditions. Moreover, the data of Table I suggest that this approach may be expected to provide routinely the NCA's of most amino acids in quantitative yield.

We have not been able to determine the optical rotations of the product NCA's because of their relatively low solubility in most organic solvents and their lability in polar solvents such as alcohols. However, reaction of **3a** in 1 N HCl affords the hydrochloride salt of alanine with $[\alpha]^{25}_D$ +8.00° (*c* 5.3, 1 N HCl). Correspondingly, the HCl salt of alanine prepared by removal of the *N*-*tert*-butoxycarbonyl group from *N*-BOC-L-Ala, used to prepare **3a**, also gave $[\alpha]^{25}_D$ +8.06° (*c* 5.3, 1 N HCl). Thus, it would appear that this metod for the preparation of *N*-carboxy anhydrides proceeds without racemization of the optically active amino acids.

Compounds **3g** and **3h**, the NCA's of N^{δ}-BOC-ornithine and N^{β}-BOC-2,3-diaminopropionate, respectively, were each prepared from their readily accessible di-BOC amino acid precursors. The sequence **1** → **3** thus affords a simple method for exclusive protection of the side-chain amino group of diamino acids, and the NCA so prepared (**4**) may be expected to serve as a versatile intermediate for the formation of amino acids (**4** → **4a**), amino acid esters (**4** → **4b**), or peptides (**4** → **4c**) which carry a protecting group *only* at the side-chain amine. In fact, we have prepared the methyl and ethyl esters of N^{β}-BOC-D,L-diamino-

(11) Compounds **3g** and **3h** are refractory to crystallization; they are isolated as oils and tend to trap THF, DMF, and *tert*-butyl chloride.

propionate by reaction of **3h** with methanol and ethanol, respectively, and subsequent tretment with 1 N HCl, to give the N^{α}-hydrochloride salts (Scheme II).

Because of our special interest in the NCA's of β-haloalanines, which have not been made previously, we prepared **3b** both by direct phosgenation of β-chloro-L-alanine and by the route **1** → **3**, using *N*-BOC-β-Cl-L-alanine as the starting material. Both methods afforded a crystalline NCA of β-Cl-L-alanine, identical with one another with reference to elution behavior on thin-layer chromatograms, infrared absorbance, and ^{1}H NMR spectrometry. But the phosgene method was more tedious, especially in workup, and the product yield was only 72%. Reaction of β-chloroalanine with trichloromethyl chloroformate did not give, in our hands, the corresponding NCA.

Experimental Section

Melting points were obtained on a Hoover Uni-melt apparatus and are uncorrected. Proton NMR spectra were obtained on a 500-MHz instrument with an internal reference of tetramethylsilane in acetone-d_6. Thin-layer chromatograms were made on Polygram Sil G silica gel. Eluting solvents were ethyl acetate (A); ethyl acetate/benzene, 1:4 (B) or 1:1 (C); acetone/benzene, 1:1 (D); or acetone (E); visualization was with iodine vapor.

All of the *N*-carboxy α-amino acid anhydrides were prepared as described below for the NCA of β-chloro-L-alanine (**3b**).[12] Analytical data are give in Table I. *N*-BOC-amino acids were either purchased from Sigma Chemical Co. or prepared by standard methods; *N*-BOC-β-Cl-L-alanine was synthesized as described previously.[9] All reagents were of the best grade commercially available.

(12) The NCA of ornithine was prepared by slight modification of our standard procedure. The reaction was carried out in 10 mL of CH_2Cl_2 and 2 equiv of oxalyl chloride were used.

***N*-Carboxy-β-chloro-L-alanine Anhydride (3b).** To a solution of *N*-BOC-β-chloro-L-alanine (400 mg, 1.8 mmol) and *tert*-butyldimethylsilyl chloride (283 mg, 1.9 mmol) in ethyl acetate (2 mL) was added triethylamine (244 μL, 1.8 mmol) at 0 °C, which gave immediate precipitation of the triethylamine hydrochloride; after 30 min of stirring at 0 °C, the triethylamine·HCl was filtered (244 mg, 100%). The filtrate was then evaporated in vacuo, giving an oil which was redissolved in 3.0 mL of CH_2Cl_2. After chilling to 0 °C, oxalyl chloride was added (195 μL, 2.25 mmol), followed by 2–3 drops of DMF. Once gas evolution subsided (approximately 2 min), additional DMF (2 drops) was added and the reaction was allowed to warm to room temperature. Additional DMF was added dropwise until no further gas evolved (approximately 10 min). The solution was then diluted with THF (~10 mL) and evaporated in vacuo; additional THF was added and the solution was evaporated once again. This routine ensures removal of any unreacted oxalyl chloride. The resulting oil was placed on a vacuum line and evaporation of DMF (over about 2 h) afforded white needles. Recrystallization from CH_2Cl_2/hexane gave the desired **3b** in 100% yield (270 mg).

Compounds were prepared for elemental analyses and melting point determination by a second recrystallization from ether/hexane (1:1) at −20 °C.

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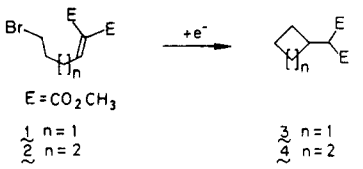
Registry No. **1a**, 15761-38-3; **1b**, 71404-98-3; **1c**, 13734-41-3; **1d**, 13734-34-4; **1e**, 7536-58-5; **1f**, 5068-28-0; **1g**, 57133-29-6; **1h**, 96165-56-9; **3a**, 2224-52-4; **3b**, 96165-57-0; **3c**, 24601-74-9; **3d**, 14825-82-2; **3e**, 13590-42-6; **3f**, 22911-82-6; **3g**, 96165-58-1; **3h**, 96165-59-2; oxalyl chloride, 79-37-8.

Communications

Intramolecular Electroreductive Cyclization[1]

Summary: Unsaturated esters, linked to a carbonyl unit by a chain of variable length, served as substrates for an investigation of intramolecular electroreductive cyclization; an efficient and reliable method for the preparation of γ-hydroxy esters has been devised.

Sir: In 1982 we reported that electroreduction of (ω-bromoalkylidene)malonates **1** and **2** led to the reasonably efficient production of cycloalkanes **3** and **4**.[3] This result suggests, as is characteristic of electroreduced olefins bearing one or more electron-withdrawing groups, that the β-carbon behaves as though it possesses nucleophilic character.[4]



(1) Dedicated to the memory of Mary Baizer.
(2) Alfred P. Sloan Foundation Fellow, 1980–1984.
(3) Nugent, S. T.; Baizer, M. M.; Little, R. D. *Tetrahedron Lett.* **1982**, *23*, 1339.

Armed with this information, we considered that a reasonable way to synthesize γ-hydroxy esters and their corresponding lactones would be to construct molecules wherein the halogen-bearing carbon in **1** and **2** was replaced by a ketone or an aldehyde.[5] Of the many structural variations which can be envisioned, two of the more interesting and potentially more useful involve the selection of both cyclic and acyclic substrates bearing a monoactivated rather than a geminal doubly activated electrophore.

We are pleased to report that an efficient and reliable

(4) This suggestion is in accord with numerous electrochemical experiments and with the results of ESR measurements which have been conducted on the radical anions of both cyclic and acyclic enones. See, for example: "Organic Electrochemistry: An Introduction and a Guide", 2nd ed.; Baizer, M. M., Lund, H., Eds.; Marcel Dekker, Inc.: New York, 1983. See also: Russell, G. A.; Stevenson, G. R. *J. Am. Chem. Soc.* **1971**, *93*, 2432. Bowers, K. W.; Giese, R. W.; Grimshaw, J.; House, H. O.; Kolodny, N. H.; Kronberger, K.; Roe, D. K. *Ibid.* **1970**, *92*, 2783.
(5) For an intermolecular variant of the present reaction, see: Shono, T.; Ohmizu, H.; Kawakami, S.; Sugiyama, H. *Tetrahedron Lett.* **1980**, *21*, 5029. Corey and Pyne have developed a nonelectrochemically based method for five-membered ring annulation which involves free radical generation from ketones using zinc–trimethylchlorosilane, followed by internal addition to a π bond. See: Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. For other examples of free radical cyclizations, refer to the review of Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883.

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