20 mmol) in THF, and ethyl 2,3-dimethyl-2-chloro-3-butenoate[11] (1.76 g, 10 mmol) to give after flash column chromatography *E* ester **3** as a colorless oil (1.55 g, 72%) eluting in 2% ethyl acetate/hexane. ^{1}H NMR: δ 1.30 (3 H, t), 1.70 (3 H, s), 1.90 (3 H, s), 3.75 (2 H, s), 4.20 (2 H, q), 7.25 (5 H, m). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.89, 142.98, 139.68, 128.93, 128.55, 128.33, 126.84, 60.51, 41.66, 19.38, 15.98, 14.30. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8.25. Found: C, 77.28; H, 8.41.

(*E*)-Ethyl 3-Phenyl-2-methyl-2-pentenoate (4).[11] To a stirred solution of CuI (2 g, 10 mmol) in THF (30 mL) at −20 °C was added a 1.6 M solution of methyllithium (14.5 mL, 20 mmol) in THF dropwise via syringe. The pale yellow solution was stirred for 15 min at −20 °C, and then a solution of **2** (2.4 g, 10 mmol) in THF (5 mL) and hexane (5 mL) was added via syringe in 1 min. The dark red solution was stirred at rt for 1 h and then poured into a mixture of ether (50 mL) and saturated ammonium chloride (20 mL). Flash column chromatography gave pure *E* ester **4** as a colorless oil (2 g, 80%) eluting in 4% ethyl acetate/hexane. ^{1}H NMR: δ 0.90 (3 H, t), 1.25 (3 H, t), 1.70 (3 H, s), 2.60 (2 H, q), 4.20 (2 H, q), 7.05–7.37 (5 H, m). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 150.58, 141.72, 128.17, 127.84, 126.95, 124.64, 60.51, 29.48, 17.38, 14.32, 12.79.

(*E*)-Ethyl 2,3-Dimethyl-2-octenoate (5).[2b] To a stirred solution of CuI (2 g, 10 mmol) in THF (30 mL) at −20 °C was added a 2.4 M solution of *n*-butyllithium (8 mL, 20 mmol) in hexane dropwise via syringe. The deep black red solution was stirred for 30 min at −20 °C, and a solution of ethyl 2,3-dimethyl-2-chloro-3-butenoate[11] (1.76 g, 10 mmol) in THF (5 mL) and hexane (5 mL) was added via syringe in 1 min. The dark green solution was stirred at rt for 2 h and then poured into a mixture of ether (50 mL) and saturated ammonium chloride (20 mL). Usual workup gave a yellow oil (2 g). Flash column chromatography gave pure *E* ester **5** as a colorless oil (1.35 g, 75%) eluting in 2% ethyl acetate/hexane. ^{1}H NMR: δ 0.90 (3 H, t), 1.25 (9 H, m), 1.75 (3 H, s), 1.85 (3 H, s), 2.25 (m, 2 H), 4.20 (2 H, q). IR (neat): 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 146.70, 122.59, 59.97, 36.41, 32.07, 28.25, 27.14, 22.64, 20.09, 15.87, 14.35.

(*E*)-Ethyl 2,3-Dimethyl-2-pentenoate (6).[11] Prepared as above from ethyl 2,3-dimethyl-2-chloro-3-butenoate (1.76 g, 10 mmol) and 1.4 M methyllithium in ether (15 mL, 20 mmol) and CuI (1.9 g, 10 mmol) to give *E* ester **6** (1.25 g, 80%) as a colorless oil eluting in 2% ethyl acetate/hexane. ^{1}H NMR: δ 0.95 (3 H, t), 1.30 (3 H, t), 1.80 (3 H, s), 1.90 (3 H, s), 2.15 (2 H, q), 4.20 (2 H, q). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 147.96, 122.35, 59.23, 29.45, 27.85, 19.55, 14.23, 12.72. Mass spectrum: *m/e* 156, 141, 127.

(*E*)-Ethyl 3-Benzyl-2-methyl-2-pentenoate (7). Prepared from ethyl 2-chloro-2-methyl-3-ethyl-3-butenoate[11] (1.9 g, 10 mmol), 2.0 M phenyllithium (10 mL, 20 mmol) in THF, and CuI (1.9 g, 10 mol) at −20 °C to give *E* ester **7** (1.75 g, 75%) eluted in 2% ethyl acetate/hexane. ^{1}H NMR: δ 1.05 (3 H, t, *J* = 7.1 Hz), 1.25 (3 H, t, *J* = 7 Hz), 1.95 (3 H, s), 2.04 (2 H, q, *J* = 7.1 Hz), 3.75 (2 H, s), 4.205 (2 H, q, *J* = 7.1 Hz), 7.20 (5 H, m). IR (neat): 1710, 1625, 1660 cm^{-1}. ^{13}C NMR: δ 169.94, 148.58, 139.71, 128.98, 128.54, 126.05, 60.51, 39.12, 25.65, 15.45, 14.24, 12.82. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.37; H, 8.55.

Ethyl 2-Methyl-3-phenyl-2-octenoate (8). ^{1}H NMR: δ 0.90 (3 H, t), 1.25 (9 H, t), 1.70 (3 H, s), 2.25 (2 H, t), 4.20 (2 H, q), 7.05–7.37 (5 H, m). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 150.58, 141.72, 128.17, 127.84, 126.95, 124.64, 60.51, 36.23, 28.25, 27.14, 22.61, 20.09, 15.85, 14.32. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.46; H, 9.23. Found: C, 78.31; H, 9.38.

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Registry No. 1, 100191-02-4; (*E*)-3, 139244-08-9; (*Z*)-3, 139244-09-0; (*E*)-4, 139244-10-3; (*Z*)-4, 139244-11-4; (*E*)-5, 67275-07-4; (*Z*)-5, 67275-08-5; (*E*)-6, 14622-00-5; (*Z*)-6, 13979-29-8; (*E*)-7, 139244-12-5; (*Z*)-7, 139244-13-6; (*E*)-8, 139244-14-7; (*Z*)-8, 139244-15-8; (*E*)-ethyl 2-methyl-3-phenyl-2-butenoate, 52094-27-6; (*Z*)-ethyl 2-methyl-3-phenyl-2-butenoate, 52094-28-7; ethyl 2-chloro-2-methyl-3-phenyl-3-butenoate, 127229-67-8; ethyl 2-chloro-2,3-dimethyl-3-butenoate, 127229-64-5; ethyl 2-chloro-3-ethyl-2-methyl-3-butenoate, 128191-95-7; $(Ph)_2CuLi$, 23402-69-9; $(Me)_2CuLi$, 15681-48-8; $(n\text{-}Bu)_2CuLi$, 24406-16-4.

The Use of Triphosgene in Preparation of *N*-Carboxy-α-amino Acid Anhydrides

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N-carboxy-α-amino acid anhydrides (NCAs), or Leuchs' anhydrides,[1] constitute a special category of mixed anhydrides which achieve both amino group protection and carboxylate activation of α-amino acids simultaneously. The apparent advantage of the concurrent amine protection and carboxylate activation in NCAs is, however, counterbalanced by their high reactivity. These reagents are sensitive to moisture and are prone to polymerization,[2] therefore, difficulties are encountered in controlling amide bond formation. The use of NCAs in biphasic carbonate buffer, as described by Japanese workers, largely overcomes this limitation.[3] In addition, the recent application of urethane-protected NCAs allows for their facile use in stepwise synthesis of peptides on solid support.[4]

N-carboxyanhydrides are often formed by the reaction of unprotected amino acids with an excess of phosgene gas.[5] The use of standardized phosgene solutions in preparation of NCAs has been reported by Fuller et al.[6] Furthermore, trichloromethyl chloroformate (diphosgene)[7] and bis(trichloromethyl)carbonate (triphosgene)[8] have both been used as phosgene precursors in reactions with unprotected amino acids at high temperatures to afford NCAs. Alternative preparations for NCAs included the reaction of urethane-protected α-amino acids with PBr_3, PCl_5, or $SOCl_2$.[9] Reaction of oxalyl chloride with the silyl esters of *N*-(*tert*-butoxycarbonyl)-α-amino acids (i.e., *N*-BOC-amino acids) to give NCAs is a milder version of the above reactions with urethane-protected amino acids.[10] Comprehensive reviews on the preparation and reactions

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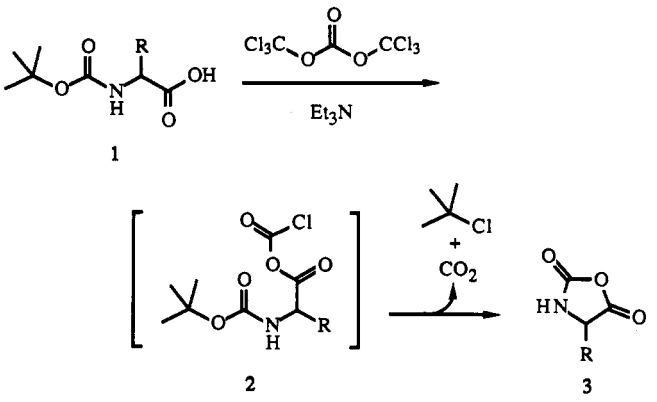
Table I. *N*-Carboxy-α-amino Acid Anhydrides Prepared

NCA	yield, %	IR,[a] cm^{-1}	mp, °C	MS,[b] *m/z*	^{1}H NMR,[c] δ
L-valine[12]	75	1855, 1785	68–69	exp + H 144.0661, (calc. 144.0665)	1.04 (d, 3 H, *J* = 6.9 Hz), 1.09 (d, 3 H, *J* = 6.9 Hz), 2.25 (m, 1 H), 4.22 (d, 3 H, *J* = 3.9 Hz), 6.71 (br s, 1 H)
O-benzyl-L-tyrosine[13]	65	1848, 1785	88–95	298 (50, M + 1)[d]	2.99 (dd, 1 H, *J* = 6.9, 14.2 Hz), 3.20 (dd, 1 H, *J* = 4.5, 14.2 Hz), 4.50–4.60 (m, 1 H), 6.0 (br s, 1 H), 6.93 (d, 2 H, *J* = 8.4 Hz), 7.14 (d, 2 H, *J* = 8.4 Hz), 7.2–7.4 (m, 5 H)
O-benzyl-L-threonine[14]	66	1868, 1786	106–107	exp 235.0845, (calc. 235.0841)	1.38 (d, 3 H, *J* = 6.3 Hz), 3.91 (quint, 1 H, *J* = 11.7 Hz), 4.19 (d, 1 H, *J* = 5.4 Hz), 4.45 (d, 1 H, *J* = 11.4 Hz), 4.65 (d, 1 H, *J* = 11.4 Hz), 5.95 (br s, 1 H), 7.3–7.4 (m, 5 H)
L-phenylalanine[15]	75	1847, 1784	91–93	exp 191.0582, (calc. 191.0578)	2.99 (dd, 1 H, *J* = 8.4, 14.1 Hz), 3.30 (dd, 1 H, *J* = 4.2 14.1 Hz), 4.56 (m, 1 H), 6.31 (br s, 1 H), 7.2–7.4 (m, 5 H)
O^γ-benzyl-L-glutamic acid[16]	72	1860, 1778 1728	78–80	264 (45, M + 1)[d]	2.09–2.30 (m, 2 H), 2.6 (t, 2 H, *J* = 6.9 Hz), 4.40 (m, 1 H), 5.14 (s, 2 H) 6.81 (br s, 1 H), 7.3–7.4 (m, 5 H)
glycine[17]	83	1859, 1787	96–98	exp 101.0113, (calc. 101.0116)	4.24 (s, 2 H)
N^ϵ-BOC-L-lysine[12]	73	1822, 1782, 1688	115 dec	217 (100, M − *t*Bu)[d]	1.45 (s, 9 H), 1.62–1.99 (m, 6 H), 3.08 (m, 2 H), 4.31–4.35 (m, 1 H), 7.17 (br s, 1 H)

[a] Film in $CHCl_3$, carbonyl stretches. [b] Electron impact (EI) or chemical ionization (CI). [c] 300 MHz, δ in ppm, downfield from tetramethylsilane, in $CDCl_3$. [d] High-resolution peak matching could not be done with these NCAs.

Scheme I



of NCAs have appeared in the literature recently.[11]

We wish to report a facile one-pot reaction for the formation of NCAs at room temperature. In a typical reaction the *N*-BOC-amino acid 1 and triphosgene are stirred in ethyl acetate at room temperature. Triethylamine addition to the solution is accompanied by an instantaneous precipitation of triethylamine·HCl salt salt to give the intermediate 2 (Scheme I). Thereafter, the progress of the reaction can readily be followed by measuring CO_2 evolution with a manometer connected to the flask. The requisite amount of CO_2 forms within 2–20 h depending on the nature of the amino acid. The choice of ethyl acetate for solvent was made since triethylamine·HCl is marginally soluble in this solvent at room temperature. Triethylamine·HCl is recovered in >95% yields by filtration of the product suspension. The NCAs listed in Table I were each prepared by this procedure. The chemical conversion of *N*-BOC-amino acids to NCAs (1 → 3) is invariably quantitative, as judged by the extent of CO_2 evolution. The losses in the overall yields are a consequence of low solubility of NCAs in most organic solvents, including ethyl acetate. At times some NCAs show a trace of triethylamine hydrochloride as an impurity [easily detected and quantified by ^{1}H NMR: δ 3.20 (q, 2 H, *J* = 7.2 Hz), 1.26 (t, 3 H, *J* = 7.2 Hz)]. The last traces of triethylamine hydrochloride can be precipitated from the solution by chilling the reaction mixture on ice–water for 5–10 min prior to filtration. However, this procedure results in somewhat lower yields for the desired NCA. If the potential contamination of the NCA by traces of triethylamine·HCl can be tolerated, the use of a larger volume of solvent in the reaction improves the recovery of NCAs.

Experimental Section

Melting points were obtained in a Hoover Uni-melt apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Nicolet DX instrument. Proton NMR spectra were obtained on a Nicolet Model QE-300 spectrometer. Mass spectral analyses were carried out on a Kratos MS 80RFA instrument.

All of the NCAs reported in Table I were prepared as described below for the NCA of valine. Analytical data for each NCA is given in Table I. All *N*-BOC-amino acids were purchased from the Peninsula Laboratories, Inc., with the exception of di-BOC-lysine which was prepared according to the method of Moroder et al.[18] Ethyl acetate was dried by storage over molecular sieves. Anhydrous triethylamine was freshly distilled prior to use.

***N*-Carboxy-L-valine Anhydride.** To a solution of *N*-BOC-*L*-valine (500 mg, 2.3 mmol) and bis(trichloromethyl)carbonate (273 mg, 0.92 mmol) in anhydrous ethyl acetate (55 mL) was added distilled triethylamine (353 mL, 2.5 mmol) over 30 s at room temperature; an immediate precipitation of Et_3N·HCl resulted. The vessel was connected to a manometer to monitor CO_2 evolution while maintaining a vigorous stirring of the reaction suspension. The requisite amount of CO_2 was generated in 3 h, at which time the suspension was filtered. The solid Et_3N·HCl was washed with a small portion of ethyl acetate (10 mL), and the filtrate was evaporated to dryness. The resulting residue was crystallized from CH_2Cl_2 and petroleum ether at −20 °C to give the title compound as white crystals (330 mg, 75%).

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