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3-Alkoxycarbonyl-2-oxazolones and Their Homopolymers as Highly Preservable Amino-Protecting Reagents. *tert*-Butoxycarbonylation and Benzyloxycarbonylation of Amino Groups

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Highly preservable amino protecting reagents derived from the 2-oxazolone moiety as a common activating mediator have been developed. 3-Alkoxycarbonyl-2-oxazolones serve as easily handled reagents for amino protection, including *tert*-butoxycarbonylation, benzyloxycarbonylation, *p*-methoxybenzyloxycarbonylation, methoxycarbonylation and ethoxycarbonylation. For example, high yield N-protection of α-amino acids has been smoothly performed by the use of 3-*tert*-butoxycarbonyl [Boc-Ox] and 3-benzyloxycarbonyl-2-oxazolones [Cbz-Ox] in aqueous solution at room temperature. A series of homopolymers, poly(3-alkoxycarbonyl-2-oxazolone), is readily obtainable by radical-initiated chain reaction of the corresponding 4,5-unsubstituted oxazolone monomers (except for the *tert*-butoxy derivative, which failed to give polymeric compounds), and these were successfully used for amino protection as well. Use of the polymer reagents greatly simplifies the purification procedure, though a longer reaction time is required.

Keywords——3-alkoxycarbonyl-2-oxazolone; poly(2-alkoxycarbonyl-2-oxazolone); 3-*tert*-butoxycarbonyl-2-oxazolone; 3-benzyloxycarbonyl-2-oxazolone; amino protection

Five- and six-membered heterocycles such as imidazole,[1] oxazolidine,[2] thiazolidine,[3] and pyridine[4] derivatives have served as important reagents in many areas of synthetic chemistry. Among them, 4,5-unsubstituted 2-oxazolone has proved to have much potential in carboxyl-activating processes as a bifunctional leaving moiety,[5] in addition to its synthetic utilization as a building block for amino alcohols.[6] The good leaving function of this simple heterocycle led to the development of 2-oxo-3-oxazolinylphosphonate and 3-acyl-2-oxazolides as versatile reagents for acyl-transfer reactions to nucleophiles.[7] Thus, various amides, including peptides and β-lactams, and thiol esters were readily prepared from the carboxylic acids by inter- and intramolecular dehydration with such reagents under mild conditions, and smooth C-acylation of activated methylene compounds was also observed. It is still of interest to explore further the synthetic potential of the 2-oxazolone moiety, which is greatly superior to 2-oxazolidinone[7] and 2-benzoxazolinone[8] heterocycles as a carboxyl-activating mediator.

This paper presents a full account of the preparation and applications of 3-alkoxycarbonyl-2-oxazolones and their homopolymers (such as **7**), which permit smooth introduction of the *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) protection groups that are widely used in peptide synthesis.

Such alkoxycarbonyl derivatives have excellent hydrolytic stability, and the by-products of the protection reactions, *viz.* deacylated oxazolones, can generally be separated quite easily from the N-blocked products owing to their high water-solubility. On the other hand, the usefulness of insoluble polymeric reagents from a preparative viewpoint is obvious, since

product purification can be achieved simply by filtering the polymer away from the reaction mixture.[9] Thus, the reagents presented herein may be preferable to most of the amino protecting agents currently available in terms of preservability (stability), purity and ease of handling.[10]

Preparation and Properties of the Reagents

The compound discussed in this paper include 3-*tert*-butoxycarbonyl, 3-benzyloxycarbonyl-, 3-*p*-methoxybenzyloxycarbonyl-, 3-methoxycarbonyl- and 3-ethoxycarbonyl-2-oxazolones, and the corresponding polymers with a carbon–carbon backbone structure (Chart 1).

The *tert*-butoxycarbonyl derivative (**2**) [Boc-Ox] was readily prepared in 80% yield by treatment of 2-oxazolone (**1**) with phosgene or trichloromethyl chloroformate followed by esterification with *tert*-butanol. Reagent **4** was similarly synthesized in 65% yield using *p*-methoxybenzyl alcohol in place of *tert*-butanol. Other alkoxycarbonyl reagents **3**, **5** and **6** could be obtained in high yields by acylation of 2-oxazolone (**1**) with the corresponding alkyl chloroformates. Reagents thus obtained are easily purified by recrystallization to give non-irritant crystals and have excellent storage characteristics (essentially no decomposition on prolonged storage without rigid exclusion of moisture). Reactivity toward hydroxyl functions was quite low and in practice, the *tert*-butoxycarbonyl compound **2** could be recrystallized from ethanol without any side reactions.

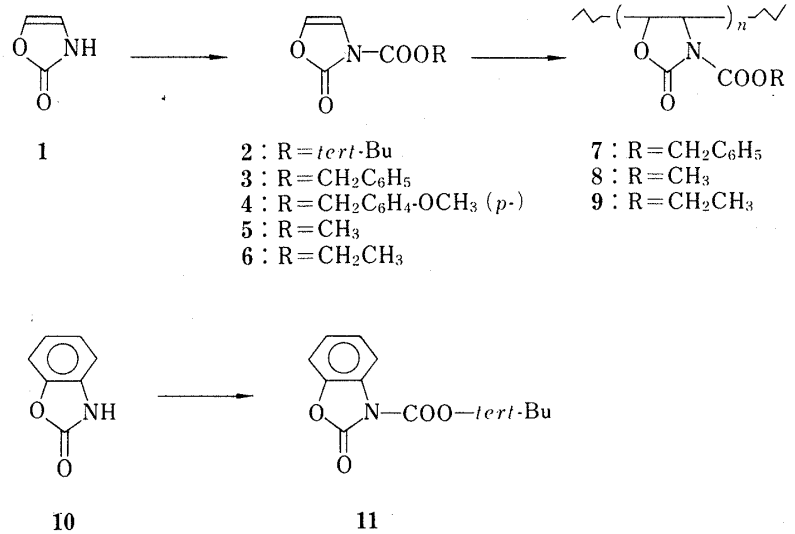


Chart 1

Radical-initiated polymerization of 3-substituted 2-oxazolone monomers such as **3**, **5** and **6** in the presence of benzoyl peroxide (BPO) proceeded smoothly to give good yields of the corresponding homopolymers **7**—**9** with a relatively low molecular weight of $\overline{Mw}$ 10300 ($\overline{Mn}$ 4000), as determined by gel permeation chromatography using tetrahydrofuran as a solvent.[11] Polymers thus obtained (as colorless powders) were insoluble in methanol, *n*-hexane and benzene, and soluble in tetrahydrofuran, acetonitrile, acetone and dimethylformamide at room temperature.

The polymeric reagents were apparently less labile than the corresponding monomers, but were still reactive enough to provide smooth protection of amines under conditions comparable to those for the monomeric reagents. The Boc-Ox derivative **2** failed to give such a homopolymer under redical-initiated conditions.[12]

***N*-Alkoxycarbonylation of Amines**

Amino protection was readily achieved merely by mixing primary and secondary amines

TABLE I. Amino-Protection by 3-Alkoxycarbonyl-2-oxazolones and Their Homopolymers[a]

Protecting group	Reagent	mp (°C)	N-Protected benzylamine	N-Protected piperidine
tert-Butoxycarbonyl	Box-Ox (**2**)	83.5	80% (4 h, DMF)	82% (4 h, DMF)
Benzyloxycarbonyl	Cbz-Ox (**3**)	86	85% (1 h, benzene)	93% (1 h, DMF)
p-Methoxybenzyloxy carbonyl	Pmz-Ox (**4**)	96	83% (1 h, THF)	98% (0.5 h, THF)
Methoxycarbonyl	Moc-Ox (**5**)	124	93% (0.5 h, THF)	74% (0.5 h, THF)
Ethoxycarbonyl	Eoc-Ox (**6**)	44	98% (0.5 h, THF)	89% (1 h, THF)
Benzyloxycarbonyl	Poly(Cbz-Ox) (**7**)	190[b]	82% (20 h, CH_3CN)[c]	80% (2 h, benzene)[d]
Methoxycarbonyl	Poly(Moc-Ox) (**8**)	300	76% (16 h, THF)[d]	—
Ethoxycarbonyl	Poly(Eoc-Ox) (**9**)	245	63% (16 h, THF)[d]	—

a) The reactions were performed at room temperature using 1.2 and 2.0 molar equivalent of the monomeric (**2**—**6**) and polymeric (**7**—**9**) reagents, respectively; the reaction time and solvent are given in parentheses.
b) Softening point. *c*) Homogeneous solution. *d*) Heterogeneous solution.

with the alkoxycarbonyl reagents (**2**—**9**) in either aprotic or protic solvents at room temperature.

Table I summarizes typical results for N-protection of benzylamine and piperidine, conducted in aprotic media with both monomeric and polymeric reagents. The reactions with monomeric reagents were almost completed at room temperature within 1 h or so, and Boc-Ox (**2**) butoxycarbonylated benzylamine ten times faster in methanol than *N-tert*-butoxycarbonyl-2-benzoxazolinone (**11**) prepared analogously. These observations demonstrate the versatility of the 4,5-unsubstituted 2-oxazolone moiety as a good activating mediator in the alkoxycarbonylation of amino groups.

The amine could also be protected by two equimolar amounts of polymeric reagents under either homogeneous (in acetonitrile) or heterogeneous (in tetrahydrofuran and benzene) conditions. Use of the polymer reagents greatly simplified the procedure for product purification and this might counterbalance the longer reaction time required for the amino protection.

N-tert-Butoxycarbonylation of α-Amino Acids

Introduction of *tert*-Boc groups was conveniently performed by the treatment of 50% aqueous dioxane (or aqueous acetone) solutions of amines with a slight excess of Boc-Ox reagent (**2**) in the presence of triethylamine containing a catalytic amount of 4-dimethylaminopyridine (DMAP). In the cases of alanine and phenylalanine, yields were heavily dependent on the presence of DMAP, which greatly enhanced the transfer reaction, acting as a catalyst.[13] Reaction times of longer than 10 h were desirable for thorough N-protection of most α-amino acids at room temperature and so the reactions were conducted in aqueous dioxane at room temperature overnight. In this way, a variety of amino acids were protected in satisfactory yields without racemization, as expected (Table II). Deacylated by-products generated during the reactions were easily removable from the N-protected products simply by washing the organic layers (such as ethyl acetate) with water under neutral conditions.

Reagent **2** gave preferential amino protection of hydroxyl amino acids such as threonine without affecting the hydroxyl groups, as expected from the precedent of the acylation reactions of 3-acyl-2-oxazolones.[7]

These properties make the Boc-Ox compound (**2**) suitable for use as an N-protecting reagent for amino acids.[14]

N-Benzyloxycarbonylation of α-Amino Acids

The Cbz-Ox reagent **3** was shown to be quite suitable for *N*-benzyloxycarbonylation of α-

TABLE II. *N-tert*-Butoxycarbonylation of α-Amino Acids by Boc-Ox Reagent (**2**)[a]

Amino acid	Base (eq) Et_3N	Base (eq) DMAP[b]	Isoalted yield (%)	mp (°C)	$[\alpha]_D$	[Lit.][c]
L-Ala	1.1	0.2	85	82	−24.4° (*c*=1, AcOH)	[−25.2°]
	0	1.5	96			
	1.5	0	51			
L-Asp	0	1.5	77	170	−9.2° (*c*=1, DMF)	[−8.5°]
Gly	1.1	0.2	81	87		
	1.5	0	86			
L-Ileu	1.1	0.3	87	126[d]	+1.9° (*c*=1, AcOH)	[−]
L-Leu	1.1	0.3	85	69	−24.4° (*c*=1, AcOH)	[−25.0°]
L-Met	1.1	0.3	82	138[d]	+15.2° (*c*=1, MeOH)	[+15.2°]
N-Nitro-L-Arg	1.1	1.0	82			
L-Phe	1.1	0.2	85	86	−3.9° (*c*=1, AcOH)	[−4.3°]
	0	1.5	93			
	1.5	0	40			
L-Pro	1.1	0.2	87	135	−59.8° (*c*=1, AcOH)	[−61.1°]
	1.1	0	92			
L-Thr	1.1	0.3	87	151[d]	+12.0° (*c*=1, MeOH)	[+11.4°]
	0	1.5	96			
L-Trp	1.1	0.2	88	134	−18.4° (*c*=1, AcOH)	[−18.2°]
L-Val	1.1	0.3	84	78	−6.5° (*c*=1, AcOH)	[−6.3°]

a) The reactions were performed with 1.5 eq of the reagent **2** in 50% aqueous dioxane at room tepmerature overnight.
b) 4-Dimethylaminopyridine.
c) Literature values. See ref. 14.
d) Determined as dicyclohexylammonium salts.

TABLE III. *N*-Benzyloxycarbonylation of α-Amino Acids by Cbz-Ox Reagent (**3**)[a]

Amino acid	Isoalted yield (%)	mp (°C)	$[\alpha]_D^{25}$	[Lit. value][b]
L-Ala	90	83	−14.5° (*c*=2, AcOH)	[−13.9°]
L-Asp	89	117	+9.0° (*c*=7, AcOH)	[+9.6°]
L-Gln	81	137	−5.4° (*c*=2, EtOH)	[−5.7°]
Gly	89	118		
L-Phe	87 (97)[c]	85	+5.5° (*c*=2, EtOH)	[+5.1°]
L-Pro	93	Oil[d]	−59.4° (*c*=5.3, AcOH)	[−61.7°]
L-Ser	88	117	+6.1° (*c*=2, AcOH)	[+5.9°]

a) The reactions were carried out in a mmol scale using 1.2 eq of the Cbz-Ox reagent **3** in 30% aqueous acetone at room temperature overnight.
b) See N. Izumiya *et al.*, "Peptide Synthesis," Maruzen Co., Ltd., Tokyo, 1975, p. 27.
c) With 2 eq of the reagent **3**.
d) Lit. mp 77 °C. The IR spectrum was identical with the spectrum reported in ref. 17.

amino acids under mild conditions. Thus, a solution of an α-amino acid in aqueous acetone was treated with a slight excess of **3** in the presence of triethylamine at room temperature to yield the N-protected amino acid. As indicated in Table III, high to excellent yields were obtained even without the use of DMAP as a catalyst. Selective amino-protection of the amino alcohols was performed as reported in the case of serine.[15]

Experimental

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) data were obtained on either a Hitachi R-24 (60 MHz) or a JEOL FX-100 (100 MHz) spectrometer in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard. Optical rotations were measured with a JASCO DIP-140 digital polarimeter in a 0.5 dm cell. High-resolution mass spectra (MS) were determined with a JEOL JMS-D-300 spectrometer equipped with a JMF-2000 data analyzer. 2-Oxazolone (**1**) was quantitatively obtained by controlled methanolysis of 3-acetyl-2-oxazolone[16] as described before.[6,7]

3-*tert*-Butoxycarbonyl-2-oxazolone [Boc-Ox] (2)——Trichloromethyl chloroformate (12.6 g, 0.064 mol) was added dropwise to an ice-cooled solution of 2-oxazolone (**1**) (9.0 g, 0.11 mol) and *N*,*N*-dimethylaniline (19.2 g, 0.16 mol) in dioxane (100 ml). The mixture was kept at 0 °C for 1 h and then at room temperature overnight, then a mixture of *tert*-butanol (15.7 g, 0.21 mol) and pyridine (16.7 g, 0.21 mol) was added dropwise at 0 °C. The whole was stirred at 0 °C for 2 h and at room temperature for another 5 h. The insoluble materials were filtered off and the filtrate was evaporated *in vacuo* to leave a yellow solid (19.0 g). The solid was dissolved in CH_2Cl_2 (200 ml) and the solution was washed successively with water, 5% hydrochloric acid and saturated NaCl solution. After removal of the solvent, the residual solid was recrystallized from CH_2Cl_2–*n*-hexane to give the reagent **2** as colorless crystals, 15.7 g (80%), mp 83—84 °C. IR (KBr): 1814, 1731 cm^{-1}. ^{1}H-NMR δ: 1.63 (s, 9H), 6.87 (d, J=2.5 Hz, 1H), 7.08 (d, J=2.5 Hz, 1H). *Anal.* Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.56. Found: C, 51.66; H, 5.95; N, 7.43.

3-Benzyloxycarbonyl-2-oxazolone [Cbz-Ox] (3)——Benzyl chloroformate (30% in toluene) (0.1 mol) was added to a solution of 2-oxazolone (**1**) (7.0 g, 0.08 mol) in pyridine (10 ml) at 0 °C and the mixture was stirred at room temperature overnight. After being diluted with CH_2Cl_2 (100 ml), the mixture was washed with 5% HCl solution twice. Evaporation of the solvent gave crystals which were recrystallized from benzene–*n*-hexane to give **3** as colorless needles (15.0 g, 83%), mp 84—86 °C. Additional product (1.1 g) was obtained by chromatography of the mother liquors; the total yield was 89%. IR (KBr): 1815, 1730 cm^{-1}. ^{1}H-NMR δ: 5.32 (s, 2H), 6.75 (d, J=2.0 Hz, 1H), 7.02 (d, J=2.0 Hz, 1H), 7.40 (s, 5H). *Anal.* Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.16; H, 4.08; N, 6.51.

3-*p*-Methoxybenzyloxycarbonyl-2-oxazolone [Pmz-Ox] (4)——In the same manner as described for compound **2**, **4** was prepared by treatment of 2-oxazolone (**1**) (2.0 g, 24 mmol) with trichloromethyl chloroformate (2.8 g, 14 mmol) followed by addition of *p*-methoxybenzyl alcohol (3.9 g, 28 mmol). Yield 65% (3.9 g), mp 95—96 °C, (from CH_2Cl_2–*n*-hexane). IR (KBr): 1824, 1719 cm^{-1}. ^{1}H-NMR δ 3.81 (s, 3H), 5.31 (s, 2H), 6.71 (d, J=2.2 Hz, 1H), 6.87 (d, J=8.0 Hz, 2H), 6.98 (d, J=2.2 Hz, 1H), 7.36 (d, J=8.0 Hz, 2H). *Anal.* Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.84; H, 4.35; N, 5.92.

3-Methoxycarbonyl-2-oxazolone [Moc-Ox] (5)——In the same manner as described for the reagent **3**, treatment of 2-oxazolone (2.1 g, 25 mmol) with methyl chloroformate (2.8 g, 30 mmol) in the presence of Et_3N (3.0 g, 30 mmol) in CH_3CN (30 ml) gave **5** as colorless crystals in 93% yield (3.3 g), mp 123—124 °C (from benzene). IR (KBr): 1833, 1810, 1716 cm^{-1}. ^{1}H-NMR δ: 3.97 (3H, s), 6.83 (d, J=2.5 Hz, 1H), 7.06 (d, J=2.5 Hz, 1H). *Anal.* Calcd for $C_5H_4NO_4$: C, 41.97; H, 3.52; N, 9.79. Found: C, 42.03; H, 3.43; N, 9.62.

3-Ethoxycarbonyl-2-oxazolone [Eoc-Ox] (6)——The use of ethyl chloroformate in place of methyl ester in the above produre gave **6** in quantitative yield (98%) as colorless plates, mp 43—44 °C (from ether–*n*-hexane). IR (KBr): 1812, 1726 cm^{-1}. ^{1}H-NMR δ: 1.41 (t, J=6.8 Hz, 3H), 4.92 (q, J=6.8 Hz, 2H), 7.04 (d, J=2.2 Hz, 1H), 7.80 (d, J=2.2 Hz, 1H). *Anal.* Calcd for $C_6H_7NO_4$: C, 45.86; H, 4.49; N, 8.92. Found: C, 45.75; H, 4.41; N, 8.77.

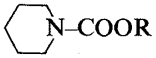
Poly(3-benzyloxycarbonyl-2-oxazolone) [Poly(Cbz-Ox)] (7)——A mixture of monomer **3** (2.2 g) and a catalytic amount of benzoyl peroxide (BPO) (0.03 g) was deaerated at room temperature and heated at 90 °C under an argon atmosphere. Within a few minutes, it started to solidify. After being kept at the same temperature for 1 h, the solid was dissolved in acetone (5 ml) and poured into MeOH (50 ml). The colorless precipitates that deposited were collected, washed well with MeOH and dried *in vacuo* at room temperature. The polymer weighed 1.65 g (75% yield), mp 180—190 °C. IR (KBr): 1820, 1730 cm^{-1}. ^{1}H-NMR (CH_3CN) δ: 4.94 (br s, 2H), 5.14 (br s, 2H), 7.25 (br s, 5H), $\overline{Mw}$ 10300 (determined by the GPC method).[11] [*Anal.* Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.00; H, 4.08; N, 6.11.]

Poly(3-methoxycarbonyl-2-oxazolone) [Poly(Moc-Ox)] (8)——In the same way as above, heating of the monomer **5** (0.8 g) at 130 °C in the presence of BPO (0.05 g) for 5 h gave the polymer in 67% yield (0.54 g) as a powder, mp 300 °C. IR (KBr): 1820, 1732 cm^{-1}.

Poly(3-ethoxycarbonyl-2-oxazolone) [Poly(Eoc-Ox)] (9)——A deaerated mixture of **6** (1.2 g) and BPO (0.02 g) gave, on heating at 75 °C for 5 h, the polymer **9** as a colorless powder (0.82 g, 68%), mp 240—245 °C (dec.). IR (KBr): 1820, 1726 cm^{-1}.

3-*tert*-Butoxycarbonyl-2-benzoxazolinone (11)——Trichloromethyl chloroformate (3.3 g, 16.6 mmol) was added to a stirred solution of 2-benzoxazolinone (**10**) (1.5 g, 17.6 mmol) and *N*,*N*-dimethylaniline (2.1 g, 17 mmol) in CH_2Cl_2 (100 ml) at 0 °C and the mixture was kept at room temperature overnight. Then a mixture of *tert*-butanol (2.5 g, 33 mmol) and pyridine (2.0 g, 25 mmol) was added at 0 °C and the resulting suspension was stirred at 5 °C for 1 h and at room temperature for 3 d. The usual work-up as described for Boc-Ox (**2**) gave the *N*-butoxycarbonylated

TABLE IV. Data for *N*-Alkoxycarbonylated Benzylamine (a) and Piperidine (b)

Compound	mp (°C) (Recry. from)	Analysis or MS (M^+) [Calcd]	IR (cm^{-1})	^{1}H-NMR (δ) (J in Hz)
a) $C_6H_5CH_2NHCOOR$				
R=*tert*-Bu	55 (*n*-Hexane)	C, 69.82; H, 8.32; N, 6.66 [C, 69.57; H, 8.21; N, 6.76]	3330 1680	1.42 (s, 9H), 4.28 (d, J=6.0, 2H) 4.5—5.1 (m, 1H), 7.23 (s, 5H)
R=$CH_2C_6H_5$	60 (*n*-Hexane)	C, 74.90; H, 6.26; N, 5.83 [C, 74.69; H, 6.22; N, 5.81]	3330 1690	4.30 (d, J=6.0, 2H), 5.08 (s, 2H) 5.40 (br s, 1H), 7.22 (s, 5H), 7.29 (s, 5H)
R=$CH_2C_6H_4$–OMe	77 (CH_2Cl_2–*n*-hexane)	C, 70.74; H, 6.30; N, 5.19 [C, 70.83; H, 6.32; N, 5.16]	3350 1687	3.78 (s, 3H), 4.35 (d, J=6.0, 2H), 5.07 (s, 2H) 4.8—5.3 (br s, 1H), 6.85 (d, J=7.8, 2H), 7.32 (d, J=7.8, 2H)
R=CH_3	57 (Ether–*n*-hexane)	C, 65.35; H, 6.75; N, 8.66 [C, 65.44; H, 6.71; N, 8.48]	3320 1702	3.61 (s, 3H), 4.27 (d, J=6.0, 2H) 4.9—5.6 (br s, 1H), 7.23 (s, 5H)
R=CH_2CH_3	39 (Ether–*n*-hexane)	C, 66.79; H, 7.24; N, 7.82 [C, 67.02; H, 7.31; N, 7.82]	3350 1686	1.21 (t, J=7.0, 3H), 4.09 (q, J=7.0, 2H), 4.29 (d, J=6.0, 2H), 4.7—5.3 (br s, 1H), 7.18 (s, 5H)
b) 				
R=*tert*-Bu	Oil	(m/z 185.1409 (M^+)) [m/z 185.1414 (M^+)]	1696	1.46 (s, 9H), 1.1—1.8 (br m, 6H) 3.1—3.6 (br m, 4H)
R=$CH_2C_6H_5$	Oil	(m/z 219.1252 (M^+)) [m/z 219.1257 (M^+)]	1698	1.3—1.7 (m, 6H), 3.25—3.60 (m, 4H) 5.07 (s, 2H), 7.26 (s, 5H)
R=$CH_2C_6H_4$–OCH_3	39 (Ether–*n*-hexane)	C, 67.60; H, 7.78; N, 5.55 [C, 67.45; H, 7.68; N, 5.62]	1687	1.4—1.9 (m, 6H), 3.25—3.65 (m, 4H), 3.29 (s, 3H) 5.02 (s, 2H), 6.84 (d, J=7.8, 2H), 7.27 (d, J=7.8, 2H)
R=CH_3	Oil	(m/z 143.0936 (M^+)) [m/z 143.0944 (M^+)]	1704	1.3—1.8 (m, 6H), 3.25—3.55 (m, 4H) 3.66 (s, 3H)
R=CH_2CH_3	Oil	(m/z 157.1101 (M^+)) [m/z 157.1101 (M^+)]	1697	1.27 (t, J=7.2, 3H), 1.35—1.80 (m, 6H), 3.2—3.65 (m, 4H), 4.12 (q, J=7.2, 2H)

derivative **11** as colorless needles (0.8 g, 20%), mp 80—81 °C (from CH_2Cl_2–*n*-hexane). IR (KBr): 1817, 1806, 1747 cm^{-1}. ^{1}H-NMR δ: 1.68 (s, 9H), 7.06—7.38 (m, 3H), 7.55—7.87 (m, 1H). *Anal.* Calcd for $C_{12}H_{13}NO_4$: C, 61.26; H, 5.57; N, 5.95. Found: C, 61.55; H, 5.58; N, 6.15.

Alkoxycarbonylation of Benzylamine and Piperidine (General Procedure)——A solution of an amine (2—4 mmol) in an aprotic solvent as indicated in Table I was treated with a monomeric reagent (**2**—**6**) (1.2 eq) at room temperature for 0.5 to 4 h. Protic solvents such as MeOH and EtOH were also effective. After removal of the solvent *in vacuo*, the oily residue was chromatographed on silica gel to give the N-blocked amine as colorless crystals or an oil.

Similar protection of amino groups could be attained by using a relatively small excess (2 eq) of a polymeric reagent (**7**—**9**); the purification procedure was greatly simplified since the excess reagents and deacylated polymers could be simply filtered off. The filtrate was worked up as above to give the N-protected amine. The results are summarized in Table I, and physical and analytical data for the products are given in Table IV.

***N-tert*-Butoxycarbonyl-benzylamine**——Benzylamine (0.09 g, 0.83 mmol) was treated with *N-tert*-Boc-**11** (0.24 g, 1 mmol) in MeOH (2 ml) at room temperature for 20 h. Removal of the solvent followed by chromatography on silica gel gave the N-protected amine, mp 50—54 °C, in only 6% yield (11 mg). In contrast, Boc-Ox reagent (**2**) gave 58% of *N-tert*-Boc-benzylamine under the same conditions.

***N-tert*-Butoxycarbonyl-α-amino Acids (General Procedure)**——Boc-Ox reagent (**2**) (1.5 mmol) was dissolved in dioxane (2 ml) and added to an aqueous solution (2 ml) of an α-amino acid (1 mmol) and Et_3N (1.1 mmol) in the presence of DMAP (0.2 mmol). The mixture was stirred at room temperature overnight (15—20 h). After removal of the dioxane *in vacuo*, the mixture was diluted with H_2O (5 ml) and then extracted with ethyl acetate (10 ml). The aqueous layer was acidified with 5% citric acid aqueous solution at 0 °C and the product was extracted with ethyl acetate (50 ml). Usual work-up gave the *N-tert*-butoxycarbonyl amino acid in satisfactory yield, as indicated in Table II. In the cases of L-asparagine and *N*-nitro-L-arginine, larger amounts of the solvent were needed due to the poor solubility. Products thus obtained were fully characterized by direct comparison with commerically available authentic specimens or by comparison of the IR spectra with reported data.[17]

A typical example is as follows. A dioxane solution (2 ml) of Boc-Ox (0.28 g, 1.5 mmol) was added to a mixture of L-valine (0.12 g, 1 mmol), Et_3N (0.11 g, 1.1 mmol) and DMAP (30 mg, 0.25 mmol) in H_2O (2 ml). The whole was stirred at room temperature overnight, then the dioxane was removed *in vacuo*. The residue was diluted with H_2O (10 ml) and washed with ethyl acetate (10 ml). The aqueous layer was acidified with 5% citric acid aq. solution at 0 °C and the product was extracted with ethyl acetate (50 ml). The organic layer was washed well with H_2O and evaporated *in vacuo* to give *N-tert*-Boc-L-valine as a solid (0.18 g, 84%), mp 78 °C (from EtOAc–petr. ether) [lit.[18] 77—79 °C], $[\alpha]_D^{25}$ −6.5° ($c=1$, AcOH) [lit.[18] −6.9°].

***N*-Benzyloxycarbonyl-α-amino Acids (General Procedure)**——A solution of Cbz-Ox reagent (**3**) (1.8 mmol) in acetone (3 ml) was added to the mixture of an α-amino acid (1.5 mmol) and Et_3N (1.6 mmol) in H_2O (5 ml) and the whole was kept at room temperature overnight. After removal of the acetone *in vacuo*, the resulting solution was washed with ethyl acetate (10 ml). The aqueous layer was acidified with 10% hydrochloric acid and extracted with ethyl acetate (30 ml) repeatedly. The extracts were evaporated *in vacuo* to give the *N*-benzyloxycarbonyl amino acid, which was further purified by recrystallization. The products thus obtained were identical with authentic specimens in terms of the IR spectra.[17]

The following example is a typical one. An aqueous acetone solution (10 ml) of L-serine (0.16 g, 1.5 mmol) was treated with Cbz-Ox (**3**) (0.4 g, 1.8 mmol) in the presence of Et_3N (0.16 g, 1.6 mmol) at room temperature overnight. Removal of the acetone *in vacuo*, followed by extraction with ethyl acetate (10 ml) gave a clear aqueous solution, which was acidified with 10% HCl solution. The product was extracted with ethyl acetate (30 ml) and the extracts were evaporated *in vacuo* to leave crystals (0.35 g). Recrystallization from $CHCl_3$ gave *N*-Cbz-L-serine as colorless needles, 0.31 g (88%), mp 117 °C [lit.[19] 119.5 °C], $[\alpha]_D^{25}$ +6.1° ($c=2$, AcOH) [lit.[19] +5.9°]. The IR spectrum (KBr) was identical with that of an authentic sample.[17]

References and Notes

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