Table I. HPLC Assay of Enantiometric Purity

cmpd	method	t_R, min	ee/de, %
L-Ser	a	17	98
D-Ser	a	13	98
8	b	20	93
epi-8	b	17	95

[a] Daicel Chiralpak WH column at 50 °C eluting with 0.25 mM aqueous $CuSO_4$ at 2.0 mL/min and employing UV detection at 254 nm. [b] 10 μm SiO_2 (25 cm × 4.5 mm) at 25 °C eluting with (20:1) hexanes–EtOAc at 2.0 mL/min and employing UV detection at 254 nm.

complished via flash chromatography on silica gel eluting with (3:2) hexanes–EtOAc and gave 90 mg (71% yield) of oxazolidine alcohol 7 as a colorless oil, $[\alpha]_D$ −24.0° (*c* 1.61, $CHCl_3$). An essentially identical procedure was applied to *ent*-5 and gave the antipode *ent*-7, $[\alpha]_D$ +23.6° (*c* 1.44, $CHCl_3$), in 64% yield: IR (neat) 3400, 1690, 1665 cm^{-1}; ^1H NMR (C_6D_6 + D_2O, 60 °C) δ 1.37 (s, 9 H), 1.43 (br s, 3 H), 1.56 (br s, 3 H), 3.51 (m, H), 3.62 (m, 3 H), 3.586 (m, H). Upon cold storage, a sample of *ent*-7 crystallized as prisms, mp 38–39 °C. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.11; H, 9.17; N, 6.06. Found: C, 56.96; H, 9.21; N, 6.10.

B. Preparation of (−)-MPTA Esters of 7 and *ent*-7. To a solution of alcohol 7 (59 mg, 0.26 mmol), DCC (60 mg, 0.28 mmol), and DMAP (3 mg, 0.03 mmol) in dry CH_2Cl_2 (1.0 mL) was added 0.77 mL of a 0.38 M stock solution of (−)-MTPA in CH_2Cl_2. After the mixture was stirred ambient temperature for 4.5 h, the TLC in (3:2) hexanes–EtOAc showed the clean formation of product 8, R_f 0.75 (UV and char B), at the expense of starting material at R_f 0.43. The resulting white suspension was filtered to remove the *N,N'*-dicyclohexylurea and then partitioned between EtOAc (20 mL) and H_2O (10 mL). The organic layer was washed with 10 mL each of 1 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine then dried with $MgSO_4$, filtered, and concentrated to give 129 mg of crude product as an oily solid. Flash chromatography on silica gel eluting with (1:1) hexanes–EtOAc yielded 119 mg (104% crude yield) of material, $[\alpha]_D$ −48° (*c* 1.87, $CHCl_3$), that was analyzed directly: IR (neat) 1760, 1705 cm^{-1}; ^1H NMR (C_6D_6, 75 °C) δ 1.39 (s, 9 H), 1.41 (br s, 3 H), 1.53 (br s, 3 H), 3.39 (d, *J* = 1 Hz, 3 H), 3.54 (dd, *J* = 9.2 and 5.8 Hz, H), 3.62 (dd, *J* = 9.2 and 1.9 Hz, H), 3.95 (m, H), 4.17 (m, H), 4.54 (dd, *J* = 10.4 and 3.2 Hz, H), 7.0–7.4 (m, 4H), 7.61 (br d, *J* = 7.9 Hz, H); ^{19}F NMR ($CDCl_3$, 20 °C) δ 4.92 (s). An essentially identical procedure was performed with *ent*-7 and resulted in the isolation of *epi*-8 (see Table I), $[\alpha]_D$ −9.7° (*c* 1.06, $CHCl_3$): IR (neat) 1750, 1700 cm^{-1}; ^1H NMR (C_6D_6, 75 °C) δ 1.41 (br s, 12 H), 1.55 (br s, 3 H), 3.38 (s, 3 H), 3.49 (dd, *J* = 9.3 and 5.6 Hz, H), 3.62 (dd, *J* = 9.3 and 1.9 Hz, H), 3.91 (m, H), 4.10 (m, H), 4.58 (dd, *J* = 10.3 and 3.4 Hz, H), 7.0–7.4 (m, 4 H), 7.60 (br d, *J* = 7.3 Hz, H); ^{19}F NMR ($CDCl_3$, 19 °C) δ 4.84 (s), 4.99 (s).

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Novel Preparation of N-Protected Amino Acid Active Esters Using 1,2,2,2-Tetrachloroethyl Carbonates

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1,2,2,2-Tetrachloroethyl chloroformate reacts with substituted phenols or *N*-hydroxy imides to yield crystalline and stable mixed aryl or oximido tetrachloroethyl carbonates. When allowed to react with an N-protected amino acid derivative, these compounds proved to be efficient for the syntheses of the corresponding active esters. A series of active esters including *p*-nitrophenol, trichlorophenol, pentafluorophenol, and *N*-hydroxysuccinimide derivatives were prepared by this new procedure.

Active esters of amino acid derivatives represent one of the most important classes of activation for peptide coupling.[1] In a preceding paper, we presented a new method for the preparation of these active esters,[2] using 2-propenyl aryl carbonates, which constituted an alternative to the classical DCC coupling of N-protected amino acids with phenols. However, this method gave moderate yields in isolated active esters and was somewhat limited by the relatively expensive cost of starting 2-propenyl chloroformate material.

Following our investigation toward the application of new chloroformates in peptide synthesis, we turned our attention toward 1,2,2,2-tetrachloroethyl chloroformate. This chloroformate is readily prepared (even on an industrial scale) by the reaction of chloral with phosgene[3a] and has been used recently for the synthesis of N-protected amino acids.[3b,c] In contrast to isopropenyl chloroformate, it is not suitable for direct mixed anhydride preparation. This is probably due to the instability of the intermediate mixed anhydride. Moreover, the chloral which is released in the reaction gives unwanted byproducts with the amino component. However, the mixed aryl or oximido tetrachloroethyl carbonates can be obtained by reaction of the

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Table I. Mixed Aryl and Oximido Tetrachloroethyl Carbonate Derivatives

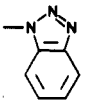
carbonate	method, yield (%)	bp, °C (torr), or mp, °C	crystn solvent	^{1}H NMR, ppm	IR, cm^{-1}	combustion anal., found (calcd)
$CCl_3CHClOCOONSu$	A, 83 B, 83	104–106 108	pet. ether Et_2O	2.9 (s) 6.6 (s)	1760	C 26.00, H 1.74, N 4.10, O 23.54, Cl 43.55 (C 25.87, H 1.55, N 4.31, O 24.6, Cl 43.55)
$CCl_3CHClOCOO(2,4,6)Tcp$	A, 64	71	pet. ether	6.73 (s) 7.4 (s)	1800	C 26.61, H 1.02, O 11.56, Cl 60.80 (C 26.54, H 0.74, O 11.78, Cl 60.93)
$CCl_3CHClOCOO(2,4,5)Tcp$	A, 92	150–155 (0.02)		6.7 (s) 7.4 (s) 7.56 (s)	1795	C 26.67, H 0.90, O 11.95, Cl 60.64 (C 26.54, H 0.74, O 11.78, Cl 60.93)
$CCl_3CHClOCOOPcp$	A, 98	120	ethyl acetate	6.7 (s)	1800	C 22.4, H traces, Cl 67.15 (C 22.66, H 0.27, Cl 67.05)
$CCl_3CHClOCOOPfp$	A, 91	80 (0.05)		6.7 (s)	1800	C 27.6, H 0.47, Cl 35.8, F 24.56, (C 27.44, H 0.26, Cl 36.00, F 24.12)
$CCl_3CHClOCOONp$	C, 75	69	pet. ether	6.7 (s) 7.5 (d) 8.36 (d)	1790	C 30.87, H 1.53, N 3.81, O 22.23, Cl 41.15 (C 30.97, H 1.44, N 4.01, O 22.92, Cl 40.64)
$CCl_3CHClOCOO(2,4)DNp$	C, 66	121–122	pet. ether	6.73 (s) 8.6 (dd) 9.06 (d) 7.66 (d)	1795	C 27.49, H 1.04, N 6.98, O 27.99, Cl 35.95 (C 27.44, H 1.02, N 7.0, O 28.43, Cl 36)
$CCl_3CHClOCOOBt$	B, 85	145–147	CH_2Cl_2	7.04 (s) 7.6 (dd) 7.8 (dd) 8.0 (d) 8.2 (d)	1770 1790	C 31.38, H, 1.37, N 12.16, Cl 41.03 (C 31.30, H 1.45, N 12.17, Cl 41.16)

Table II. (*tert*-Butyloxycarbonyl)amino Acid *N*-Succinimidyl Esters

				literature			
Boc-amino acid-OSu	yield, %	mp, °C	$[\alpha]^{22}_D$	yield, %	mp, °C	$[\alpha]_D$ (*c*, solvent)	ref
Gly	91	168		62	168–170		4
Ala	94	158	−50.7	71	143–144 or 167	−49.0 (2, dioxane)	4
Phe	91	147–149	−19.8	81	152–153	−19.0 (2.2, dioxane)	4
Val	92	125–127	−37.4	74	128–129	−37.0 (2, dioxane)	4
Pro	82	133–134	−54.7	74	135–136	−55.3 (2, dioxane)	4
Tyr	74	180–181	−12.1		180–182	−12.5 (1, dioxane)	5
Trp	89	151–152	−23.1		153–154	−22.4 (1, dioxane)	4
Met	92	127–128	−21.6	59	128–129	−20.6 (2, dioxane)	4
Tyr(Bzl)	73	149–150	−6.2		149–150	−6.3 (2, dioxane)	6c
Cys(Bzl)	61	115–116	−54.0	49	117–117.5	−54.0 (2, dioxane)	4
Lys(Z)	85	109–110	−21.5		109–110	−21.1 (2, dioxane)	6c
Ser(Bzl)	78	110–112	+5.8	52	112–113	+6.5 (0.5, dioxane)	7
Thr(Bzl)	85	91–93	+9.4		94	+8.5 (1, dioxane)	8

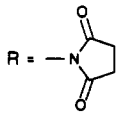
above chloroformate with phenols or *N*-hydroxy imides according to reaction 1. These derivatives are able to

$$Cl_3CCHClOCOCl + ROH \longrightarrow Cl_3CCHClOCOOR \quad (1)$$

R =  , C_6Cl_5, C_6F_5, 2,4,5-$C_6H_2Cl_3$, 2,4,6-$C_6H_2Cl_3$, 4-$C_6H_4NO_2$, 2,4-$C_6H_3(NO_2)_2$, 

produce active ester derivatives in the presence of a carboxylate (reaction 2). They have been found to be much

$$RCOOH + Cl_3CCHClOCOOR \longrightarrow RCOOR + CO_2 + Cl_3CCHO \quad (2)$$

R =  , C_6Cl_5, C_6F_5, 2,4,5-$C_6H_2Cl_3$

more suitable than the previously described aryl 2-propenyl carbonates for active ester synthesis of amino acid derivatives.

The mixed carbonate preparation has been performed by using 2,4,5- and 2,4,6-trichlorophenols, pentachlorophenol, pentafluorophenol, *p*-nitrophenol, 2,4-dinitrophenol, *N*-hydroxysuccinimide, and *N*-hydroxybenzotriazole. Yields are generally good and allowed large-scale preparations. The reaction with *N*-hydroxyphthalimide gave a mixture of the expected product together with 10% of diphthalimido carbonate. The reaction of 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine gave an untractable mixture. Their physical properties are reported in Table I. The carbonates are usually crystalline and stable and can be stored at room temperature.

Some of these carbonates readily react with protected amino acid derivatives to yield the corresponding active esters, CO_2 and chloral. As chloral is quantitatively transformed to the water-soluble hydrate on hydrolysis, this new method provides a very clean, simple, and efficient method for active ester preparation. Compared to the classical preparation using DCC, elimination of the DCU filtration is an actual improvement. The results of the syntheses of various active ester derivatives are reported in Tables II–V. The best results were obtained with *N*-oxysuccinimidyl, 2,4,5-trichlorophenyl, and pentafluorophenyl derivatives; *p*nitrophenyl and pentachlorophenyl derivatives react sluggishly. Melting points and optical rotation were in good agreement with the lit-

Table III. (Benzyloxycarbonyl)amino Acid *N*-Succinimidyl Esters

				literature			
Z-amino acid-OSu	yield, %	mp, °C	$[\alpha]^{22}_D$	yield, %	mp, °C	$[\alpha]^{22}_D$ (*c*, solvent)	ref
Z-Ala	86	121–123	−36.9	65	123–123.5	−37.2 (2, dioxane)	4
Z-Cys(Bzl)	81	90–91	−54.0	92	90–91	−58.5 (2, dioxane)	9
Z-Gly	93	113–114			113–114		4
Z-Lys(Boc)	92	97–99	−16.1	74	96–98	−15.9 (2, dioxane)	10
Z-Met	93	101–102	−16.2	59	101–102	−15.9 (2, dioxane)	4
Z-Phe	96	139–141	−17.5	76	140–140.5	−17.3 (1, dioxane)	4
Z-Pro	97	88–90	−54.9	74	90	−54 (1, dioxane)	4
Z-Tyr(Bzl)	82	144–145	−49.8		144–145	−50.5 (1, DMF)	11

Table IV. (*tert*-Butyloxycarbonyl)amino Acid 2,4,5-Trichlorophenyl Esters

				literature			
Boc-amino acid-OTcp	yield, %	mp, °C	$[\alpha]^{22}_D$	yield, %	mp, °C	$[\alpha]_D$ (*c*, solvent)	ref
Gly	95	106–107		86	107–108		12
Ala	79	81–82	−38.5	73	81–82	−39 (2.0, DMF)	12
Phe	96	120–121	−25.8	70	122	−27.0 (2.0, DMF)	12
Val	93	59–61		91	58–60		13
Pro	87	58–60	−42.4	90	60–61.5	−40.8 (2.0, MeOH)	14
Cys(Bzl)	60	77–78		86	77–78		13
Glu(OBzl)	60	106–108	−33.5	60	106–108	−33.5 (2.0, MeOH)	15
Lys(Z)	85	98–99	−19.1	86	98–99		13
Met	79	90–91	−38.0	71	90–91	−38.5 (18 DMF)	16
Ser	22	103–104	−42.0	5	104–105	−41.0 (1, DMF)	17
Tyr	73	168	−31.4	40	156–158	−26.4 (2, AcOEt)	15

Table V. (*tert*-Butyloxycarbonyl)amino Acid Pentafluorophenyl Esters

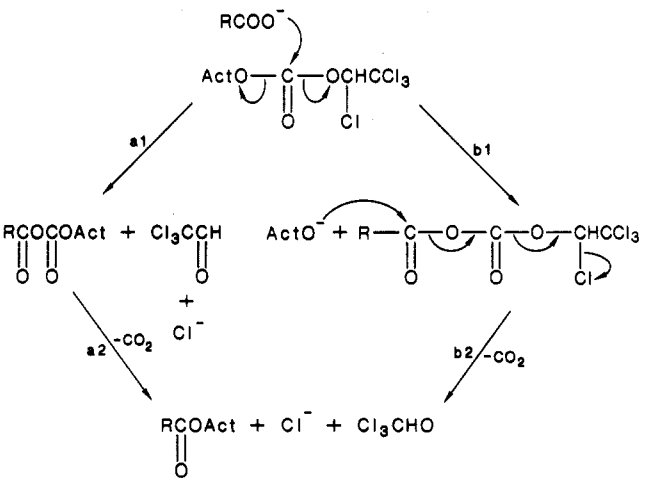
				literature[18]		
Z-amino acid-OPfp	yield, %	mp, °C	$[\alpha]^{22}_D$	yield, %	mp, °C	$[\alpha]_D$ (*c*, solvent)
Gly	90	79–80		70	79–80	
Ala	90	83–85	−34.6	85	82–83	−31.2 (1.08 dioxane)
Phe	86	112	−16.8	97	111–112	−26.9 (1.0, dioxane)
Val	90	60–64	−31.8	78	62–64	−18.4 (1.0, dioxane)
Pro	88	48–51	−48.2	88	51–52	−53.0 (1.0, dioxane)
Cys(Bzl)	91	99–101	−39.1	78	99–101	−42.0 (1.0, dioxane)
His(DNp)	90	109	+5.8		108–110	+6.8 (1.0, dioxane)
Lys(Z)	91	54	−16.9	80	54–55	−17.1 (1.0, dioxane)
Trp	91	111	−12.8	88	109–111	−28.1 (1.0, dioxane)

erature data. However, some pentafluorophenyl esters give significant deviations from the literature values. In our hands, reproduction of the described preparation using DCC confirms our data, but we cannot ascertain the absence of racemization in these cases. We assume however that these deviations are due to the pentafluorophenyl esters themselves rather than to the reagent. As described in the literature, 2,4-dinitrophenyl esters and *N*-oxybenzotriazolyl esters are very reactive and not very stable.

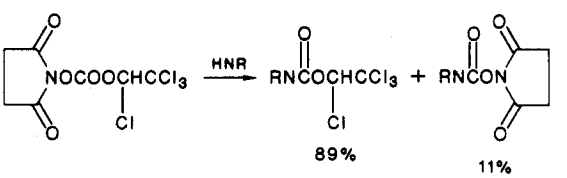
The reaction proceeds by initial attack of the carboxylate on the central carbonyl and release of either chloral and chloride ion or *N*-oxysuccinimide (or phenate) anion (Scheme I, steps a1 or b1). We have observed that when morpholine was allowed to react with 1,2,2,2-tetrachloroethyl *N*-succinimidyl carbonate, 1,2,2,2-tetrachloroethyl *N*-morpholinecarboxylate and *N*-succinimidyl morpholinecarboxylate were formed in an 89/11 ratio (Scheme II). Although the reaction is quite different, we assume that *N*-oxysuccinimide should be the best leaving group and route b1–b2 is the preferred mechanism. However, the transient oxyanion liberated in b1 can act as a catalyst for the completion of the reaction through the a1–a2 route.

In conclusion, this new method provides an easy preparation of N-protected amino acid active ester derivatives using cheap reagents, in a reaction where the byproduct is water soluble and easily eliminated from the reaction mixture.

Scheme I



Scheme II[a]



[a] RNH = morpholine.

Experimental Section

Capillary melting points are reported uncorrected. Thin-layer chromatograms (TLC) were performed on silica gel plates (Merck). Optical rotations were measured with Perkin-Elmer 241 MC polarimeter. Elemental analyses were performed by "Le Centre de Microanalyse du CNRS", ENSCM, Montpellier and ICSN, Gif

sur Yvette. ^1H NMR spectra (60 MHz) were recorded on a Varian EM 360 A or (360 MHz) on a Bruker 360 spectrometer, at 25 °C, using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Abbreviations used were those recommended by the IUPAC–IUB Commission (*Eur. J. Biochem.* **1984**, *138*, 9–37).

General Procedure for the Synthesis of Mixed Aryl or *N*-Hydroxyaryl Tetrachloroethyl Carbonates. Method A. 1,2,2,2-Tetrachloroethyl chloroformate (12.35 g, 0.05 mol) was added to a stirred solution of the hydroxy compound (0.05 mol) in dichloromethane (50 mL). The reaction mixture was cooled to 0 °C, and pyridine (4 g, 0.05 mol) was added dropwise. The solution was allowed to warm at room temperature and stirred for 3 h. After addition of dichloromethane (150 mL), the reaction mixture was washed with cold water (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo, and the residual product was distilled or crystallized as described in Table I.

Method B. In this method, pyridine was replaced by triethylamine. The reaction mixture was allowed to react for 1 h at 0 °C and then 2 h at room temperature. The reaction mixture was then treated as described in method A.

Method C. The required phenol (0.1 mol) was added to a mechanically stirred solution of 1,2,2,2-tetrachloroethyl chloroformate (27 g, 0.11 mol) in a mixture of benzene (150 mL) and light petroleum ether (150 mL). The suspension was cooled to 0 °C, and triethylamine (11 g, 0.11 mol) was added dropwise with vigorous stirring. The reaction mixture was allowed to warm to room temperature and stirring was continued for 4 h. After filtration on Celite, the solution was concentrated in vacuo and the crystalline residue was rinsed with light petroleum ether and dried (Table I).

***N*-(*tert*-Butyloxycarbonyl)-L-alanine Pentachlorophenyl Ester.** 1,2,2,2-Tetrachloroethyl pentachlorophenyl carbonate (2.27 g, 5 mmol) was added to a solution of *N*-(*tert*-butyloxycarbonyl)-L-alanine (0.84 g, 5 mmol) and triethylamine (0.7 mL, 5 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature for 2 h. Ethyl acetate (20 mL) was then added, and the organic solution was washed with a cold 10% citric acid solution (10 mL), then with a saturated potassium bicarbonate solution (10 mL), and finally with water (10 mL). The organic solution was dried on magnesium sulfate and evaporated in vacuo. The solid residue was crystallized from ethyl acetate/petroleum ether (2.06 g, 94%): mp 170 °C (lit.[6a] mp 166 °C); $[\alpha]^{25}_D$ −24.5° (*c* 1.0, $CHCl_3$) (lit.[6a] $[\alpha]^{25}_D$ −22.2° (*c* 5.1, $CHCl_3$)).

***N*-(*tert*-Butyloxycarbonyl)-L-phenylalanine *p*-Nitrophenyl Ester.** 1,2,2,2-Tetrachloroethyl *p*-nitrophenyl carbonate (0.87 g, 2.5 mmol) was added to a solution of *N*-(*tert*-butyloxycarbonyl)-L-phenylalanine (0.73 g, 2.75 mmol) and *N*-methylmorpholine (0.3 mL, 2.5 mmol) in THF (6 mL). The reaction mixture was stirred at room temperature for 1 h. Ethyl acetate (15 mL) was then added, and the organic solution was washed with a cold 10% citric acid solution (5 mL), then with a saturated potassium bicarbonate solution (5 mL), and finally with water (5 mL). The organic solution was dried on magnesium sulfate and evaporated in vacuo. The solid residue was crystallized from 95% ethanol (0.6 g, 62%): mp 128 °C (lit.[6b] mp 132 °C); $[\alpha]^{25}_D$ −20.9° (*c* 2.0, DMF) (lit.[6b] $[\alpha]_D$ −21.0° (*c* 2.0, DMF)).

General Procedure for the Synthesis of Amino Acid Active Ester Derivatives. To a solution of the N-protected amino acid (0.10 mol) in tetrahydrofuran (120 mL) or acetonitrile, containing *N*-methylmorpholine (0.11 mol), was added the mixed aryl or imide 1,2,2,2-tetrachloroethyl carbonate derivative (0.10 mol). The reaction mixture was stirred at room temperature for 2–5 h. Ethyl acetate (500 mL) was added and the solution thoroughly washed with a 10% cold citric acid solution (1 × 100 mL), cold water (1 × 100 mL), a cold saturated bicarbonate solution (1 × 100 mL), and cold water (2 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo at $t < 40$ °C. The residue, treated with the appropriate solvents (as given in the literature), leads usually to crystalline N-protected amino acid active esters. Their purity was ascertained by TLC in different solvents as indicated in the literature. They were identified by elemental analysis and comparison of their physical properties with those reported by other authors. The physical data of the synthesized N-protected amino acid active ester derivatives are reported in Tables II–V.

Reaction of 1,2,2,2-Tetrachloroethyl *N*-Succinimidyl Carbonate with Morpholine. A solution of 1,2,2,2-tetrachloroethyl *N*-succinimidyl carbonate (1.63 g, 5 mmol) in THF (3 mL) was slowly added to a solution of morpholine (0.87 g, 10 mmol) in 3 mL of THF. The reaction mixture was stirred for 1 h and washed successively with 1 N HCl, 10% $NaHCO_3$, and water. The solution was dried over magnesium sulfate, evaporated to dryness, and the resulting product (9.5 g) examined by NMR: δ 6.8 (1 H, OCHCl), 3.4–3.8 (8.6 H, CH_2 of morpholine), 2.7 (0.5 H, CH_2 of succinimide). This is in accord with an 89/11 ratio of respectively 1,2,2,2-tetrachloroethyl *N*-morpholinecarboxylate and *N*-succinimidyl morpholinecarboxylate.

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