References and Notes

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N-Alkoxycarbonyl-*N*,*N*,*N*-trialkylammonium Fluoroborates. Formation of Carbonic Anhydrides in Peptide Synthesis

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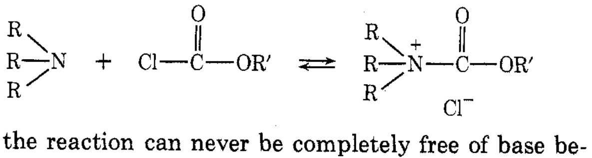
A variety of *N*-alkoxycarbonyl-*N*,*N*,*N*-trialkylammonium fluoroborates have been synthesized from tertiary amines and alkyl chloroformates. The salts are stable and can be used in the mixed anhydride method of peptide synthesis. The yields of peptides are similar to those observed previously but the amount of racemization is apparently reduced as determined by the Anderson test. The salts also react readily with primary and secondary amines to give urethanes.

The occurrence of simple *N*-alkoxycarbonyl-*N*,*N*,*N*-trialkylammonium salts has been postulated many times[3-8] but stable salts have been isolated only rarely.[9-11] The highly stabilized derivatives of 4-(*N*,*N*-dimethylamino)pyridine[10] and *N*-methylimidazole[11] may not even be in a strict sense *N*-alkoxycarbonylammonium salts. Thus there remains only the report of simple *N*-alkoxycarbonylammonium salt preparation by reaction of urethanes with methyl fluorosulfonate[9] followed by rearrangement.

Our interest in preparing the *N*-alkoxycarbonylammonium salts required preparation of wide variety of structures and high yields for use in the mixed anhydride method of peptide synthesis. We felt that if such salts can be made and used then the mixed anhydride method would be completely free of excess bases (in the formation of the mixed anhydride) that might lead to racemization.[12] Currently the *N*-alkoxycarbonylammonium salts are prepared by mixing tertiary amino and alkyl chloroformates.[12-16] Chloride ion is a fairly good nucleophile;

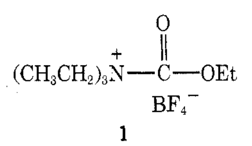


thus the reaction can never be completely free of base because the reaction is always somewhat reversible. If the reagents can be readily formed then it also may be useful in the formation of N, O, and S protecting groups.

To eliminate the problem of reversibility we chose to exchange the chloride for fluoroborate. The fluoroborate ion is less nucleophilic[17] and in our experience yields stable, nonhydroscopic salts.[18,19]

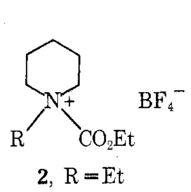
The adducts of tertiary amines and alkyl chloroformates were obtained by mixing the two reactants in ether at −78°. The addition compounds were generally observed as colorless crystals and appeared stable at room temperature under ether. Detailed examination by nmr spectroscopy and elemental analysis indicated that the substances were usually a mixture.

The anion exchange reaction was facile when the HF/BF_3 mixture was added to the adducts of tertiary amines and alkyl chloroformates at −78°. Stirring until room temperature was reached gave colorless crystals of *N*-alkyloxycarbonylammonium fluoroborates (1–12) in 89–99% yield. Most salts showed sharp melting points and varied in their stability. The pyridine derivatives were very unstable, and among those derived from aliphatic amines the stability increased as the alkyl groups became bulkier. The derivatives of *N*,*N*-dimethylcyclohexylamine and isopropyl, *sec*-butyl, or isobutyl chloroformate were the most stable *N*-alkyloxycarbonylammonium salts, allowing easy

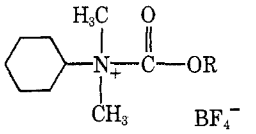


$(CH_3CH_2)_3\overset{+}{N}-C(=O)-OEt\ \ BF_4^-$

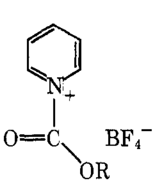
1



2, R = Et
3, R = *n*-Pr
4, R = *n*-Bu



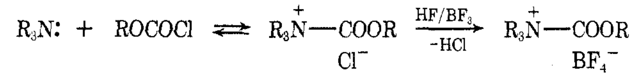
5, R = Et
8, R = CH$_2$Ph
9, R = *i*-Bu
11, R = *s*-Bu
12, R = *i*-Pr



6, R = Et
7, R = CH$_2$Ph
10, R = *i*-Bu

handling under ordinary available anhydrous experimental conditions.

The reaction scheme of the anion exchange reaction is formulated as shown below. The adduct of a tertiary



$$R_3N: + ROCOCl \rightleftarrows \underset{Cl^-}{R_3\overset{+}{N}—COOR} \xrightarrow[-HCl]{HF/BF_3} \underset{BF_4^-}{R_3\overset{+}{N}—COOR}$$

amine and an alkyl chloroformate is assumed to be the ionic intermediate from which the *N*-alkyloxycarbonylammonium fluoroborate is formed upon the addition of HF/BF$_3$ mixture by losing one HCl molecule.

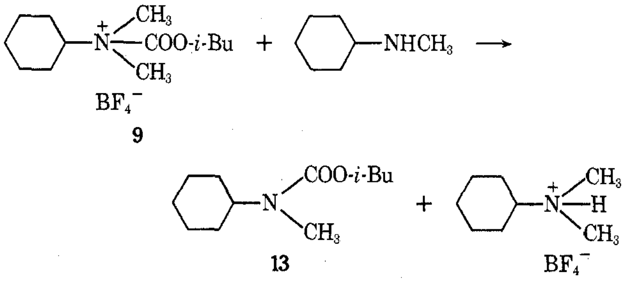
The main feature of the infrared spectra of *N*-alkyloxycarbonylammonium fluoroborates (**1**–**12**) is that each has a strong carbonyl bond absorption at around 1812–1822 cm^{-1} (except the salt **8**). Since alkyl chloroformates usually absorb strongly at around 1760–1880 cm^{-1} owing to the carbonyl bonds,[20] the carbonyl absorptions of *N*-alkyloxycarbonylammonium fluoroborates are higher by about 10–20 cm^{-1}. This is a trend similar to that observed in the infrared spectra of *N*-cyanoammonium fluoroborates.[18]

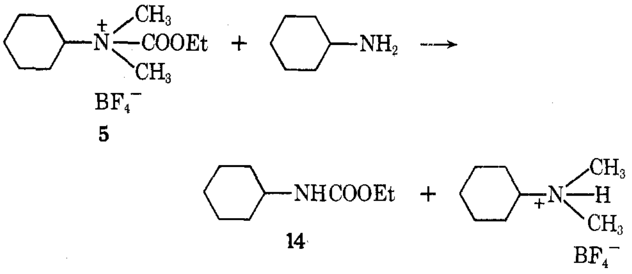
Nuclear magnetic resonance spectra of *N*-alkyloxycarbonylammonium fluoroborates were consistent with the proposed structures. The alkyl groups derived from alkyl chloroformates appeared in a chemical shift region similar to those of alkyl chloroformates. The protons adjacent to the nitrogen atom showed a drastic change in chemical shifts when comparing the *N*-alkyloxcarbonylammonium salts with ordinary tertiary ammonium salts. The chemical shifts (δ) were about 3.8 ppm for methylene protons, 3.2–3.45 ppm for methyl protons, and 4.0–4.3 ppm for methine protons in acetone-d_6. For tertiary ammonium salts the values are about 3.0, 2.95, and 3.1 ppm, respectively.

The present method of preparation of *N*-alkyloxycarbonylammonium fluoroborates using HF/BF$_3$ mixture resulted in several failures. The products obtained from *N*-methylpiperidine, trimethylamine and quinuclidine, and isobutyl chloroformate were crystalline substances, but too unstable to be characterized. In the other extreme, the reactions of most hindered tertiary amines and alkyl chloroformates were too slow at the low temperatures employed to give crystalline products. Thus, the reaction of *N*,*N*-dimethyl-*tert*-butylamine, tri-*n*-butylamine, and *N*,*N*-diethylcyclohexylamine with ethyl or isobutyl chloroformate did not give the desired products.

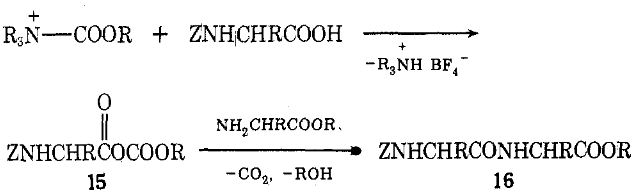
It was apparent that the alkyl groups of the alkyloxycarbonylammonium fluoroborates could be cleaved by the attack of a nucleophile as observed in several intermediates[3-9,12-16] but the cleavage of the alkyloxycarbonyl groups was also expected as in the reaction of *N*-cyanoammonium fluoroborates.[18,19] The present study dealt only with the acyl group cleavages, especially the suitability of these ammonium salts as mixed anhydride and urethane forming reagents.

The reaction of *N*-isobutyloxycarbonyl-*N*,*N*-dimethylcyclohexylammonium fluoroborate (**9**) with *N*-methylcyclohexylamine gave a 93% yield of the carbamate **13**. *N*-Ethyloxycarbonyl-*N*,*N*-dimethylcyclohexylammonium fluoroborate (**5**) reacted with cyclohexylamine to give a 99% yield of the carbamate **14**. From the two examples it is clear that urethanes can be formed in high yield using reagents. The use as selective urethane-forming reagents is being explored.





The attempted peptide synthesis using *N*-alkyloxycarbonylammonium fluoroborates proceeded to give moderate yields of oligopeptides. The carboxyl group of the N-protected amino acid attacks on the alkyloxycarbonyl group of the ammonium salt to form the mixed anhydride **15**, which is attacked by the added N-terminal amino acid to form the dipeptide derivative[16] accompanied by the liberation of carbon dioxide and an alcohol. The procedure



$$R_3\overset{+}{N}—COOR + ZNHCHRCOOH \xrightarrow[-R_3\overset{+}{N}H\ BF_4^-]{}$$

$$\underset{\mathbf{15}}{ZNHCHR\overset{\overset{\large O}{\|}}{C}OCOOR} \xrightarrow[-CO_2,\ -ROH]{NH_2CHRCOOR} \underset{\mathbf{16}}{ZNHCHRCONHCHRCOOR}$$

of this peptide synthesis was that of the generally known "mixed anhydride method" using directly tertiary amines and alkyl chloroformates. Thus, the reaction was done at about −10°, and the solution was kept overnight after the addition of the N-terminal amino acids. In most cases crystallizable products were obtained, and the best yields were observed with the isobutyl (**9**), isopropyl (**12**), and *sec*-butyl (**11**) derivatives of *N*,*N*-dimethylcyclohexylamine. The results are recorded in Tables I and II.

Table I lists the coupling reagents, solvents, and yield of the indicated products. The first four entries constitute a limited test of various coupling reagents keeping the same solvent. Entries 7 and 8 constitute the Anderson test using two coupling reagents. In general there does not seem to be any advantage to use of IBAF or IPAF, the two most promising reagents, as they give similar yields in all cases. Table II is a test for coupling of Z-Gly-OH and H-Gly-OEt under identical conditions in a variety of solvents. Since the yields are 71–90% and no effort has been made to optimize the yield, there does not seem to be any significant advantage in any solvent. The yields are generally comparable with those of original mixed anhydride method where the alkyl chloroformates are used directly.[14] The similar yields can probably be explained as being due to similar or essentially the same reaction mechanism.

Table I

	C-Terminal Amino Acid	N-Terminal Amino Acid	Coupling reagent	Solvent	Peptide product	Yield, %
1	Z-Gly-OH	Gly-OEt	IBAF (**9**)	DMF	Z-Gly-Gly-OEt	90
2	Z-Gly-OH	Gly-OEt	SBAF (**11**)	DMF	Z-Gly-Gly-OEt	83
3	Z-Gly-OH	Gly-OEt	EAF (**5**)	DMF	Z-Gly-Gly-OEt	60
4	Z-Gly-OH	Gly-OEt	IBPF (**10**)	DMF	Z-Gly-Gly-OEt	34
5	Z-DL-Val-OH	Gly-OEt	IBAF (**9**)	DMF	Z-DL-Val-Gly-OEt	80
6	Z-DL-Val-OH	Gly-Gly-OEt·HOAc/TEA[a]	IBAF (**9**)	DMF	Z-DL-Val-Gly-Gly-OEt	76
7	Z-Gly-L-Phe-OH	Gly-OEt	IBAF (**9**)	THF	Z-Gly-L-Phe-Gly-OEt (all L)	89
8	Z-Gly-L-Phe-OH	Gly-OEt	IPAF (**12**)	THF	1-Gly-Phe-Gly-OEt (3% DL, the rest L)	97
9	Z-Gly-OH	L-Phe-OEt·HCl/TEA[a]	IBAF (**9**)	CH_3CO_3Et	Z-Gly-L-Phe-OEt	74
10	Z-Gly-OH	Gly-OEt·HCl/TEA[a]	IPAF (**12**)	CH_3CO_2Et	Z-Gly-Gly-OEt	69
11	Z-Gly-OH	Gly-OEt·HCl/TEA[a]	IPAF (**12**)	CH_3CN	Z-Gly-Gly-OEt	73

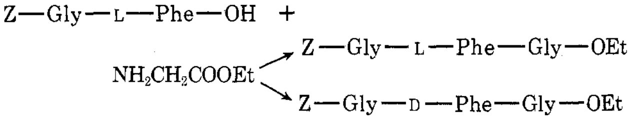
[a] TEA: triethylamine.

Table II

$$\text{Z-Gly-OH} + \text{HGly-OEt} \xrightarrow{\text{IBAF}} \text{Z-Gly-Gly-OEt}$$

Solvent	Yield, %
DMF	90
$CHCl_3$	81
THF	83
$CHCl_2$	78
CH_3CN	71
CH_3CO_2Et	77

The use of *N*-alkyloxycarbonylammonium fluoroborates in peptide synthesis was expected to give low racemization owing to the presence of reduced amounts of excess base. Excess base may arise from several sources if chloride is the anion: (1) inexact stoichiometry in weighing of the components; (2) reaction of *N*-alkyloxycarbonylammonium chlorides to give free base and chloroformate, *i.e.*, the reverse of the formation reaction; (3) ionization of the tertiary ammonium salt formed during the formation of the mixed anhydride. In all three cases the use of stable *N*-alkyloxycarbonylammonium fluoroborates will reduce the amount of free base that is present. Under ideal conditions as described by Kemp, Bernstein, and Rebek, the mixed anhydride method may show as little as 0.01% racemization.[12b] Departure from exact stoichiometry results in a greater than tenfold increase in racemization.[12b] To test the degree of racemization of this method, Anderson's method[21] was chosen among other methods.[22-24] This method has been known to be able to detect at least about 2% of racemization.[24,25] According to the procedure,[21] carbobenzoxyglycyl-L-phenylalanine was coupled with glycine ethyl ester using *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate (**9**) and yielding 89% of the tripeptide; racemized product could be obtained from this tripeptide by fractional crystallization. However, when isopropyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate (**12**) was used the yield of crude product was 97%, from which about 3% of the racemized product crystallized out. The differences observed for the two reagents are barely significant considering the sensitivity of the test. However, it is highly significant that the overall amount of racemization was very low.[25]



$$\text{Z—Gly—L—Phe—OH} + \text{NH}_2\text{CH}_2\text{COOEt} \rightarrow \text{Z—Gly—L—Phe—Gly—OEt} + \text{Z—Gly—D—Phe—Gly—OEt}$$

More sensitive tests for racemization will be needed to determine if in fact *N*-alkoxycarbonyl-*N,N,N*-trialkylammonium fluoroborates have any advantages in decreasing racemization. The first results reported here look very promising. Because the reagents are readily prepared in high yield and can be stored for months at room temperature with a little care to keep them dry, the mixed anhydride reactions will be much easier to run on a routine basis. Finally, the possibility of introducing benzyloxycarbonyl and *tert*-butyloxycarbonyl protecting groups with the same reagents adds considerably to the utility of the reagents. All aspects of the chemistry of *N*-alkoxycarbonyl-*N,N,N*-trialkyammonium fluoroborate are still under study.

Experimental Section[26]

General Procedure for the Preparation of *N*-Alkoxycarbonyl-*N,N,N*-trialkylammonium Fluoroborates. To a solution of chloroformate (0.02 mol) in 50 ml of ether cooled to −78° was added in drops a solution of tertiary amine (0.01 mol) in 50 ml of ether while stirring. It was allowed to stand for 5 hr at −78° and for 2 hr at −10 to 20°. The adduct was cooled to −78°, and a 1:1 mixture of condensed hydrogen fluoride which had been added to boron trifluoride etherate (0.015 mol) was added at once. (A stock solution of HF/BF_3 in ether could be prepared and kept in a polyethylene bottle.) After the cooling bath was removed the solution was stirred until room temperature was reached. Precipitated colorless crystals were collected, washed with ether three times, and dried under vacuum.

***N*-Ethyloxycarbonyl-*N,N,N*-triethylammonium Fluoroborate (Yield 92%).** The crystals were very unstable, and their ir and nmr spectra showed some decomposition: ir (Nujol mull) 1822 (strong, C═O) and 1000–1100 cm^{-1}; nmr (acetonitrile) δ 1.35 (t, CH_3, 9 H), 3.70 (q, CH_2N^+, 6 H), and 4.65 (q, CH_2O, 2 H).

***N*-Ethyloxycarbonyl-*N*-ethylpiperidinium fluoroborate** (yield 86%) had mp 34–35°; ir (Nujol mull) 1817 (strong, C═O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.54 (t, CH_33H), 1.50–2.20 (br, CH_2, 6 H), 3.84 (q, CH_2N^+, 2 H), 3.22–4.37 (br, CH_2N^+, 4 H), and 4.75 (q, CH_2O, 2 H).

Anal. Calcd for $C_{10}H_{20}NO_2BF_4$ (273.09): C, 43.89; H, 4.39; N, 5.13. Found: C, 43.70; H, 7.40; N, 5.40.

***N*-Ethyloxycarbonyl-*N,n*-propylpiperidinium fluoroborate** (yield 91%) had mp 32–33°; ir (Nujol mull) 1812 (strong, C═O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 0.98 (t, CH_3, 3 H), 1.48 (t, CH_3, 3 H), 1.70–2.24 (br, CH_2, 6 H), 3.40–4.40 (br, CH_2N^+, 6 H), and 4.75 (q, CH_2O, 2 H).

Anal. Calcd for $C_{11}H_{22}NO_2BF_4$ (287.04): C, 46.03; H, 7.70; N, 4.88. Found: C, 46.30; H, 7.90; N, 4.97.

***N*-Ethyloxycarbonyl-*N*-*n*-butylpiperidinium fluoroborate** (yield 96%) had mp 65–66°; ir (Nujol mull) 1812 (strong C═O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 0.95 (t, CH_3, 3 H), 1.48 (t, CH_3, 3 H), 1.60–2.24 (br, CH_2, 6 H), 3.40–4.40 (br, CH_2N^+, 6 H), and 4.75 (q, CH_2O, 2 H).

Anal Calcd for $C_{12}H_{24}NO_2BF_4$ (301.14): C, 47.86; H, 8.03; N, 4.65. Found: C, 48.10; H, 8.00; N, 4.53.

***N*-Ethyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 99%) had mp 108°; ir (Nujol mull) 1812 (strong, C═O) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.47 (t, CH_3, 3 H), 1.60–2.40 (br, CH_2, 10 H), 3.42 (s, CH_3N^+, 6 H), 3.80–4.15 (br, CHN^+, 1 H), and 4.67 (q, CH_2O, 2 H).

Anal. Calcd for $C_{11}H_{22}NO_2BF_4$ (287.10): C, 46.02; H, 7.73; N, 4.88. Found: C, 46.00; H, 7.60; N, 4.80.

***N*-Benzyloxycarbonylpyridinium fluoroborate** (yield 98%) had mp 100–100.5°; ir (Nujol mull) 1822 (strong, $C=O$) and 1000–1120 cm^{-1}; the compound decomposed when dissolved in most usually available organic solvents and on storing.

***N*-Ethyloxycarbonylpyridinium fluoroborate** (yield 95%) had mp 62–63°; ir (Nujol mull) 1822 (strong, $C=O$) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.50 (t, CH_3, 3 H), 4.80 (q, CH_2O, 2 H), 8.38 (t, 3-H, 2 H), 9.07 (t, 4-H, 1 H), and 9.67 (d, 2-H, 2 H).

Anal. Calcd for $C_8H_{10}NO_2BF_4$ (238.99): C, 40.20; H, 4.22; N, 5.86. Found: C, 40.40; H, 4.43; N, 5.76.

***N*-Benzyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 98%) had mp 90–91°; ir (Nujol mull) 1796 (strong, $C=O$) and 1030–1100 cm^{-1}; nmr ($CDCl_3$) δ 0.92–2.10 (br, CH_2, 1 OH), 3.44 (s, CH_3N^+, 6 H), 3.44–3.96 (br, CHN^+, 1 H), 5.55 (s, CH_2O, 2 H), and 7.43 (m, phenyl ring, 5 H).

Anal. Calcd for $C_{16}H_{24}NO_2BF_4$ (349.18): C, 55.03; H, 6.93; N, 4.01. Found: C, 55.30; H, 7.27; N, 3.96.

***N*-Isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 96%) had mp 50–50.5°; ir (Nujol mull) 1812 (strong, $C=O$) and 1000–1100 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (d, CH_3, 6 H), 1.20–2.35 (br, CH_2 and CH, 11 H), 3.33 (s, CH_3N^+, 6 H), 3.45–4.0 (br, CHN^+, 1 H), and 4.33 (d, CH_2O, 2 H).

Anal. Calcd for $C_{13}H_{26}NO_2BF_4$ (315.17): C, 49.54; H, 8.32; N, 4.45. Found: C, 49.80; H, 8.50; N, 4.49.

***N*-Isobutyloxycarbonylpyridinium fluoroborate** (yield 98%) had mp 69.5–70°; ir (Nujol mull) 1822 (strong, $C=O$) and 1020–1130 cm^{-1}; nmr (acetone-d_6) δ 1.08 (d, CH_3, 6 H), 2.30 (m, CH, 1 H), 4.57 (d, CH_2O, 2 H), 8.37 (t, 3-H, 2 H), 9.02 (t, 4-H, 1 H), and 9.61 (d, 2-H, 2 H). The nmr spectrum showed some decomposition.

Anal. Calcd for $C_{10}H_{14}NO_2BF_4$ (267.02): C, 44.95; H, 5.28; N, 5.25. Found: C, 44.60; H, 5.39; N, 5.45.

***N*-*sec*-Butyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 98%) had mp 81.5–82°; ir (Nujol mull) 1822 (strong, $C=O$) and 1000–1130 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (t, CH_3, 3 H), 1.46 (d, CH_3, 3 H), 1.77 (q, CH_2, 2 H), 1.20–2.30 (br, CH_2, 10 H), 3.28 (s, CH_3N^+, 6 H), 3.50–4.0 (br, CHN^+, 1 H), and 5.16 (m, CHO, 1 H).

Anal. Calcd for $C_{13}H_{26}NO_2BF_4$ (315.17): C, 47.86; H, 8.02; N, 4.65. Found: C, 47.80; H, 7.90; N, 4.76.

***N*-Isopropyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate** (yield 99%) had mp 91–92.5°; ir (Nujol mull) 1812 (strong, $C=O$) and 1000–1100 cm^{-1}; nmr (acetone-d_6) δ 1.50 (d, CH_3, 6 H), 1.40–2.18 (br, CH_2, 10 H), 3.40 (s, CH_3N^+, 6 H), 3.70–4.20 (br, CHN^+, 1 H), and 5.33 (m, CHO, 1 H); uv (acetonitrile), no absorptions between 240 and 400 nm.

Anal. Calcd for $C_{12}H_{24}NO_2BF_4$ (301.14): C, 47.86; H, 8.02; N, 4.65. Found: C, 47.80; H, 7.90; N, 4.76.

Reaction of *N*-Ethyloxycarbonyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with Cyclohexylamine. To a solution of 0.55 g (0.0019 mol) of *N*-ethyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 10 ml of methylene chloride was added 0.17 g (0.0017 mol) of cyclohexylamine. The solution was allowed to stand for 1 hr at room temperature, and the solvent was removed on a rotary evaporator. The residue was extracted with ether (3 × 20 ml) and the ether portion was washed with a small amount of water. Evaporation of the solvent gave 0.29 g (99%) of crude *N*-cyclohexylcarbamic acid ethyl ester, mp 54–56.5° (lit.[27] mp 57°); ir and nmr spectra were in agreement with the structure.

Anal. Calcd for $C_9H_{17}NO_2$ (171.24): C, 63.12; H, 10.00; N, 8.18. Found: C, 62.85; H, 9.90; N, 8.27.

Reaction of *N*-Isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium Fluoroborate with *N*-Methylcyclohexylamine. To a solution of 1.65 g (0.0053 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate in 10 ml of acetonitrile was added 0.57 g (0.005 mol) of *N*-methylcyclohexylamine at −10°. The solution was allowed to stand for several hours at room temperature, and the solvent was removed on a rotary evaporator without heating. The residue was extracted with ether (3 × 100 ml), and the ether portion was washed with a small amount of water, dried (Na_2SO_4), and distilled to give 1.01 g (93%) of oil as residue. Hickman still distillation [87° (0.35 mm)] gave 0.88 g of a clear oil of *N*-methylcyclohexylcarbamic acid isobutyl ester: ir (thin film) 1665 cm^{-1} (strong, $C=O$); nmr (CCl_4) δ 0.91 (d, CH_3, 6 H), 1.17–2.03 (br, CH_2, 10 H), 2.70 (s, CH_3, 3 H), 3.75 (d, CH_2, 2 H), and 3.80 (br, CH, 1 H).

Anal. Calcd for $C_{12}H_{23}NO_2$ (213.31): C, 67.56; H, 10.87; N, 6.57. Found: C, 67.78; H, 10.60; N, 6.45.

Reaction of *N*-Alkyloxycarbonylammonium Fluoroborates with *N*-Benzyloxycarbonyl Amino Acids. Synthesis of *N*-Benzyloxycarbonylglycylglycine Ethyl Ester. To a cooled (−10°), stirred solution of 2 09 g (0.01 mol) of *N*-benzyloxycarbonylglycine in 20 ml of dimethylformamide was added in small portions 4.20 g of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate. The mixture was stirred for 15 min at −10° and for 15 min at room temperature, and cooled to −10°. To this 1.31 g (0.013 mol) of ethyl glycinate was added in small portions while stirring. The solution was allowed to stand for 1 day at ordinary temperature followed by the removal of the solvent on a rotary evaporator. The residue was dissolved in 75 ml of ethyl acetate and washed with 25 ml of water, 25 ml of 5% $NaHCO_3$ solution, 25 ml of 1 *N* HCl solution, and 25 ml of water. It was dried (Na_2SO_4) and evaporated to give a syrupy residue which was crystallized when triturated with petroleum ether. The yield was 2.64 g (90%) of *N*-benzyloxycarbonylglycylglycine ethyl ester whose ir and nmr spectra were in agreement with those reported, mp 78–90° (lit.[28] mp 77–85°).

Anal. Calcd for $C_{14}H_{18}N_2O_5$ (294.30): C, 57.13; H, 6.16; N, 9.52. Found: C, 57.30; H, 6.31; N, 9.45.

The same procedure was followed using different solvents to give the yields indicated in Table I.

Synthesis of *N*-Benzyloxycarbonyl-DL-valylglycine Ethyl Ester. The same procedure was followed with 1.25 g (0.005 mol) of *N*-benzyloxycarbonyl-DL-valine, 2.10 g (0.0066 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 0.77 g (0.006 mol) of ethyl glycinate in 20 ml of dimethylformamide to give 1.40 g (80%) of *N*-benzyloxycarbonyl-DL-valylglycine ethyl ester: mp 147–150°; ir (Nujol mull) 1742 (strong, CO), 1690 (strong, $C=O$), and 3240 cm^{-1} (strong, NH); nmr ($CDCl_3$) δ 0.93 (br, CH_3, 6 H), 1.23 (t, CH_3, 3 H), 2.03 (m, CH, 1 H), 3.59 (d, CH_2, 2 H), 3.59 (br, CH, 1 H), 4.17 (q, CH_2, 2 H), 5.09 (s, CH_2, 2 H), 5.83 (d, NH, 1 H), 7.10 (br, NH, 1 H), and 7.30 (m, phenyl ring, 5 H).

Anal. Calcd for $C_{17}H_{24}N_2O_5$ (336.38): C, 60.70; H, 6.98; N, 8.17. Found: C, 60.70; H, 6.90; N, 8.20.

Synthesis of *N*-Benzyloxycarbonyl-DL-valylglycylglycine Ethyl Ester. The same procedure was followed with 1.25 g (0.005 mol) of *N*-benzyloxycarbonyl-DL-valine, 1.80 g (0.0057 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 1.20 g (0.0055 mol) of ethyl glycylglycinate [prepared by hydrogenolysis of *N*-benzyloxycarbonylglycylglycine ethyl ester using Pd/C (10%) as catalyst[29]] with 0.55 g (0.0055 mol) of triethylamine in 20 ml of dimethylformamide to give 1.50 g (76.2%) of *N*-benzyloxycarbonyl-DL-valylglycylglycine ethyl ester, recrystallized from ethanol: mp 119–120°; ir (Nujol mull) 3321, 3000, 1753, 1737, 1692, 1667, 1646 cm^{-1} (all sharp); nmr ($CDCl_3$) δ 0.97 (two d, CH_3, 6 H), 1.23 (t, CH_3, 3 H), 3.93 (t, CH_2, 4 H), 4.13 (q, CH_2, 2 H), 3.93–4.13 (br, NH, 1 H), 5.83 (s, CH_2, 2 H), 6.03 (d, NH, 1 H), and 7.30 (m, phenyl ring, 5 H).

Anal. Calcd for $C_{19}H_{27}N_3O_6$ (393.43): C, 58.00; H, 6.92; N, 10.68. Found: C, 58.33; H, 6.80; N, 10.48.

Synthesis of *N*-Benzyloxycarbonylglycyl-L-phenylalanine. The same procedure was followed with 4.10 g (0.0196 mol) of *N*-benzyloxycarbonylglycine, 6.52 g (0.021 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 4.0 g (0.02 mol) of ethyl L-phenylalaninate hydrochloride with 2.02 g of triethylamine in 100 ml of ethyl acetate to give 5.50 g (74%) of an amorphous product. It was dissolved in 50 ml of 1 *N* NaOH solution containing 10 ml of methanol, and stirred for 2 hr to hydrolyze. The solution was acidified with 1 *N* HCl solution (Congo Red), and the solvent was removed to give an amorphous residue which was crystallized from 1:5 acetone–water mixture. The yield was 4.50 g (90%) of *N*-benzyloxycarbonylglycyl-L-phenylalanine: mp 126–127° (lit.[21] mp 127.5°); ir (Nujol mull) 3326, 1735, 1690, 1650 cm^{-1} (all sharp); nmr (acetone-d_6) δ 3.03–3.25 (m, CH_2, 2 H), 3.83 (d, CH_2, 2 H), 4.78 (m, CH, 1 H), 5.10 (s, CH_2, 2 H), 6.40–6.80 (br, NH, 1 H), 7.23 (m, phenyl ring, 5 H), 7.33 (m, phenyl ring, 5 H), 7.33 (br, NH, 1 H), 916–9.66 (br, COOH, 1 H),

Anal. Calcd for $C_{19}H_{20}N_2O_5$ (356.37): C, 64.03; H, 5.66; N, 7.86. Found: C, 63.83; H, 5.66; N, 7.73.

Synthesis of *N*-Benzyloxycarbonylglycyl-L-phenylalanylglycine Ethyl Ester. The same procedure was followed with 3.60 g (0.0101 mol) of *N*-benzyloxycarbonylglycyl-L-phenylalanine, 3.45 g (0.011 mol) of *N*-isobutyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 1.15 g (0.011 mol) of ethyl glycinate in 30 ml of tetrahydrofuran (dried over lithium aluminum hydride) to give 3.93 g (89.2%) of an amorphous product. It was dissolved in 192 ml of absolute ethanol (2% solution) and kept in a refrigerator at about −5°.[21] After about 2 weeks the crystallization of the L tripeptide began: the small fraction was collected, which melted at 119.2–119.7° (lit.[21] mp 116.5–119.5°). Continuous refrigeration gave more crystals of the same material. The residual peptide was obtained by reducing the volume of the solution amounting to 3.50 g, and about 0.26 g of oil was left uncrystallized: ir (Nujol mull) 3225, 1750, 1715, 1688, 1665, 1650 cm^{-1} (all sharp); nmr ($CDCl_3$) δ 1.20 (t, CH_3, 3 H), 3.05 (d, CH_2, 2 H), 3.70–3.93 (two d, CH_2, 4 H), 4.10 (q, CH_2, 2 H), 4.83 (d, CH, 1 H), 5.05 (s, CH_2, 2 H), 5.85 (br, NH, 1 H), 7.15 (br, NH, 1 H), 7.15 (s, phenyl ring, 5 H), and 7.30 (s, phenyl ring, 5 H).

Anal. Calcd for $C_{23}H_{27}N_3O_5$ (441.47): C, 62.57; H, 6.17; N, 9.52. Found: C, 62.80; H, 6.04; N, 9.40.

The above procedure was followed with 3.56 g (0.01 mol) of *N*-benzyloxycarbonylglycyl-L-phenylalanine, 3.30 g (0.011 mol) of *N*-isopropyloxycarbonyl-*N,N*-dimethylcyclohexylammonium fluoroborate, and 1.15 g (0.011 mol) of ethyl glycinate in 30 ml of tetrahydrofuran. The yield of the amorphous tripeptide derivative was 4.30 g (97%). A 2% solution of the peptide in absolute ethanol gave, after about 3 weeks of refrigeration, the first fraction of crystals amounting to 0.13 g (3%) of DL tripeptide melting at 129–130° (lit.[21] mp 132–133°). After 2 days 0.07 g of crystals was obtained melting at 120–121°, and soon the L tripeptide began to appear amounting to 3.12 g, melting at 119–120.5°. The residue was obtained in crude crystals. The elemental analysis of this product was identical with that of the product in the first part of this synthesis.

Registry No.—**1**, 51157-30-3; **2**, 51056-73-6; **3**, 51108-18-0; **4**, 51056-75-8; **5**, 51056-77-0; **6**, 51056-79-2; **7**, 51056-81-6; **8**, 51056-83-8; **9**, 51056-85-0; **10**, 51056-87-2; **11**, 51108-20-4; **12**, 51056-89-4; triethylamine, 121-44-8; *N*-ethylpiperidine, 766-09-6; *N,N*-dimethylcyclohexylamine, 98-94-2; pyridine, 110-86-1; *N*-*n*-propylpiperidine, 5470-02-0; *N*-*n*-butylpiperidine, 4945-48-6; ethyl chloroformate, 541-41-3; benzyl chloroformate, 501-53-1; isobutyl chloroformate, 543-27-1; *sec*-butyl chloroformate, 17462-58-7; isopropyl chloroformate, 108-23-6; cyclohexylamine, 108-91-8; *N*-methylcyclohexylamine, 100-60-7; *N*-benzyloxycarbonylglycine, 1138-80-3; *N*-benzyloxycarbonyl-DL-valylglycine ethyl ester, 7801-65-2; *N*-benzyloxycarbonyl-DL-valine, 3588-63-4; *N*-benzyloxycarbonyl-DL-valylglycylglycine ethyl ester, 51056-90-7; *N*-benzyloxycarbonylglycyl-L-phenylalanine, 1170-76-9; *N*-benzyloxycarbonylglycyl-L-phenylalanylglycine ethyl ester, 2073-59-8.

References and Notes

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N-Acyl-*N,N,N*-Trialkylammonium Fluoroborates. Synthesis and Reactions

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Stable *N*-acyl-*N,N,N*-trialkylammonium fluoroborates have been prepared from tertiary amines and acyl halides followed by exchange of anion to fluoroborate with HF/BF_3. The stable salts react with various nucleophiles such as amines, acids, alcohols, and thiols to form the acylated derivatives. The primary alcohols react rapidly, the secondary alcohols only partially, and tertiary alcohols do not react at all.

N-Acyl-*N,N,N*-trialkylammonium salts have been examined extensively for a variety of purposes.[3-6] The salts that have been examined have been highly reactive and quite frequently impure, precluding detailed examination of their structure and properties.[7-13] The best evidence was obtained by ir from adducts prepared at liquid nitrogen temperatures.[14] However, even these showed adsorptions at around 2300–2700 cm^{-1}, indicating that the hydrohalides were present.[15] Preparation by alkylation of amides was only partially successful.[16] Thus while the compounds have been prepared in impure form many times and have been assumed as intermediates in many other reactions,[17-20] very little can be accepted without some reservations.

Our interest in *N*-cyano- and *N*-alkyloxycarbonyl *N,N,N*-trialkylammonium salts[2] as reagents in peptide synthesis led us to consider *N*-acylammonium salts as possible reagents for preparation of protecting groups. In *N*-acylammonium salts the size of the tertiary amine can be readily varied, thus allowing the possibility of stereoselective acylating reagents. We assumed from our previous experience[2] that the major cause of instability was the nucleophilic nature of the anion, which could regenerate the tertiary amine, thus allowing dehydrohalogenation