(69%), was 99% *E* isomer by ^{19}F NMR, mp 60–62 °C. (Total yield of both isomers, 77%.)

The reaction was considerably less selective when run at 0 °C giving 72% *E* isomer [bp 112–113 °C (200 mm)] and 28% *Z* isomer [bp 124–125 °C (200 mm)] in 57% yield.

Photostationary State of *E* and *Z* Isomers of *S*-Methyl 2,2,2-Trifluoro-*N*-hydroxythioacetimidate. A 6% solution of *S*-methyl (*E*)-2,2,2-trifluoro-*N*-hydroxythioacetimidate in $CDCl_3$ was irradiated with a Hanovia 450-W medium-pressure mercury arc lamp through a water-cooled quartz filter. After 20 min of irradiation, a photostationary state consisting of 27% *E* isomer and 73% *Z* isomer was reached (analysis by ^{19}F NMR). A 6% solution of the pure *Z* isomer was irradiated under the same conditions and reached the same photostationary state in 2 h. *Z* Isomer: $\lambda_{max}^{CH_2Cl_2}$ = 242 nm (*E* 5100). *E* Isomer: $\lambda_{max}^{CH_2Cl_2}$ = 252 nm (ϵ 7530).

***S*-Ethyl (*E*)-2,2,2-Trifluoro-*N*-hydroxythioacetimidate.** Ethanethiol, 17 mL (0.23 mol), was added dropwise to a solution prepared by dissolving 4.14 g (0.18 mol) of sodium in 150 mL of methanol. The reaction mixture was cooled to −70 °C, and 43.83 g (0.18 mol) of **6** was added dropwise. The reaction mixture was stirred at ambient temperature for 3 days, filtered to remove precipitated sodium chloride, and evaporated to dryness under reduced pressure. The residue was sublimed at 50 °C (1-mm pressure), and the sublimate was condensed in a cold (−78 °C) receiver and then pressed between layers of filter paper to give 15.7 g (50%) of colorless crystals: mp 28–30 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, *J* = 7 Hz, 3 H), 2.89 (q, *J* = 7 Hz, 2 H), 8.64 (OH).

The UV spectrum of this *E* isomer gave $\lambda_{max}^{CH_2Cl_2}$ 2550 Å (ϵ 7310), as contracted to the corresponding *Z* isomer, which gave $\lambda_{max}^{CH_2Cl_2}$ 2430 Å (ϵ 3320).

***N*,*N*-Dimethyl-2,2,2-trifluoroacetohydroximamide (15).** A solution of 29.5 g (0.2 mol) of **2** in 30 mL of ether was added dropwise to a solution of 22.5 g (0.5 mol, 33 mL at 0 °C) of dimethylamine in 300 mL of ether cooled to −70 °C. The reaction mixture was allowed to warm to 25 °C stirred 18 h, and then filtered to remove the precipitated dimethylamine hydrochloride. The filtrate was distilled to give 26.74 g (86%) of **15** as a colorless liquid: bp 66–67 °C (10 mm); ^{19}F NMR ($CDCl_3$) δ −65.8 (s); ^{1}H NMR ($CDCl_3$) δ 3.03 (s). Anal. Calcd for $C_4H_7F_3N_2O$: C, 30.77; H, 4.52; F, 36.51; N, 17.95. Found: C, 31.21; H, 4.85; F, 36.53; N, 18.15.

***N*-(Perfluorobutyryl)-*O*-(trifluoroacetyl)hydroxylamine (4a).** Trifluoroacetic anhydride, 54.6 g (0.26 mol), was added dropwise to a 57.3-g (0.25 mol) sample of perfluorobutyrohydroxamic acid.[10] The reaction mixture became warm and liquified. The trifluoroacetic acid that formed and the excess trifluoroacetic anhydride were distilled off at reduced pressure (1 mm at 25 °C), and the solid residue was recrystallized from methylene chloride under nitrogen to give 57.07 g (70%) of **4a** as colorless crystals: mp 39–41 °C; ^{19}F NMR (CD_3CN) δ −73.5 (s, 3 F), −80.8 (t, *J* = 9 Hz, 3 F), −120.5 (q, *J* = 9 Hz, 2 F), −127.1 (s, 2 F). Anal. Calcd for $C_6HF_{10}NO_3$: C, 22.17; H, 0.31; F, 58.45; N, 4.31. Found: C, 22.20; H, 0.67; F, 58.28; N, 4.37.

2-Chloro-2-(trifluoromethyl)-5-(perfluoropropyl)-1,3,4-dioxazole (6a). A mixture of 49.25 g (0.15 mol) of **4a** and 41.66 g (0.2 mol) of phosphorus pentachloride was heated until the reaction mixture liquified and evolution of HCl ceased. Distillation gave 18.35 g (28%) of **6a** as a colorless liquid, bp 85–92 °C, contaminated with some $POCl_3$. An analytical sample was prepared by washing with water, drying (Al_2O_3), and redistilling to give a purified sample: bp 90–91 °C; n_D^{25} 1.3036; IR (liquid) 1647 cm^{-1} (C═N); ^{19}F NMR (CCl_3F) δ −81.0 (t, *J* = 9 Hz, 3 F), −82.4 (s, 3 F), −116.1 (m, 2 F), −127.0 (s, 2 F). Anal. Calcd for $C_6ClF_{10}NO_2$: C, 20.98; Cl, 10.32; F, 55.31; N, 4.08. Found: C, 21.17; Cl, 10.36; F, 55.24; N, 4.74.

***S*-Trifluoromethyl 2,2,2-Trifluoro-*N*-hydroxythioacetimidate (14).** A mixture of 40.28 g (0.1 mol) of mercury trifluoromethylmercaptide[11] and 14.7 g (0.1 mol) of **2** was heated at reflux for 18 h. The volatile portion of the reaction mixture was distilled under reduced pressure into a cold trap (−78 °C) and then redistilled to give 6.55 g (31%) of **14** as a colorless liquid: bp 108–110 °C; IR (liquid) 3546, 3367 (OH), 1605 cm^{-1} (C═N); ^{19}F NMR (CCl_3F) δ −36.4 (q, *J* = 4.2 Hz, 3 F) and −68.1 (q, *J* = 4.2 Hz, 3 F); ^{1}H NMR (CCl_3F) δ 9.70 (s).

Registry No. 1, 32990-21-9; **2**, 815-03-2; (*Z*)-**3** (R = CH_3), 82985-93-1; (*E*)-**3** (R = CH_3), 82985-94-2; (*Z*)-**3** (R = CH_3CH_2), 82985-97-5; (*E*)-**3** (R = CH_3CH_2), 88326-75-4; (*Z*)-**3** (R = $CH_3CH_2CH_2$), 82986-00-3; (*Z*)-**3** (R = $(CH_3)_2CH$), 82985-99-7; (*Z*)-**3** (R = phenyl), 82986-02-5; (*Z*)-**3** (R = CH_2═$CHCH_2$), 82986-03-6; (*Z*)-**3** (R = *n*-butyl), 88326-76-5; (*Z*)-**3** (R = *tert*-butyl), 82986-01-4; (*Z*)-**3** (R = furfuryl), 88326-77-6; (*Z*)-**3** (R = benzyl), 88326-78-7; **4**, 684-78-6; **4a**, 88326-80-1; **5**, 82817-12-7; **6**, 82985-92-0; **6a**, 88326-81-2; **7**, 707-71-1; **8**, 88326-82-3; **10**, 86657-10-5; **14**, 88326-79-8; **15**, 88326-83-4; $(CF_3CO)_2O$, 407-25-0; $NH_2OH{\cdot}HCl$, 5470-11-1; $CF_3CO_2CH_3$, 431-47-0; CF_3CN, 353-85-5; $(CH_3)_2NH$, 124-40-3; $(CF_3S)_2Hg$, 21259-75-6; benzonitrile, 100-47-0; 2,2,2-trifluoroacetamide *O*-benzoyloxime, 88326-84-5; benzoyl chloride, 98-88-4; trifluoroacetohydroximamide, 4314-35-6; perfluorobutyrohydroxamic acid, 87050-96-2; methanethiol, 74-93-1; ethanethiol, 75-08-1; 1-propanethiol, 107-03-9; 2-propanethiol, 75-33-2; benzenethiol, 108-98-5; allyl mercaptan, 870-23-5; *n*-butyl mercaptan, 109-79-5; *tert*-butyl mercaptan, 75-66-1; furfuryl mercaptan, 98-02-2; benzyl mercaptan, 100-53-8; trifluoromethanethiol, 1493-15-8.

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Notes

Active Esters of Polymer-Bound 4-Hydroxy-3-nitrobenzophenone as Useful Acylating Reagents. Application to Peptide Synthesis

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Received January 22, 1982

Polymeric active esters have found considerable use as acylating reagents in peptide synthesis,[1,2] preparation of semisynthetic penicillins and cephalosporins,[3] studying intrapolymer interactions,[4] and in multipolymer reactions with carbanions.[5] They are easily separated from low molecular weight reactants by filtration or selective pre-

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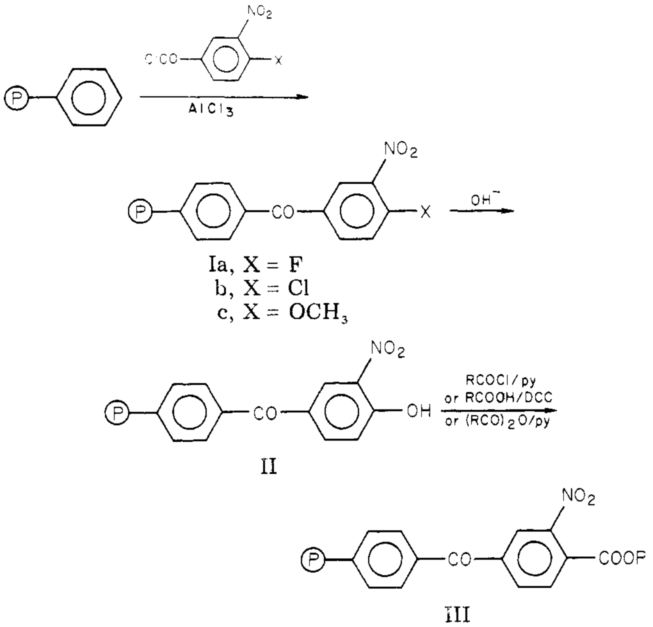
Scheme I



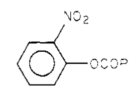
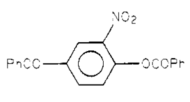
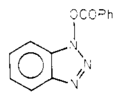
cipitation, can be used in excess to effect fast and quantitative acylations, and are usually recyclable. Previously prepared in this laboratory were two such polymeric reagents, namely, active esters of polymer-bound *o*-nitrophenol[6] and N^1-hydroxybenzotriazole.[7] The first is prepared in a single step from polystyrene, but coupling reactions of its active esters with free amino peptides require hours for completion. Active esters of the second polymer, prepared in a three-step modification of polystyrene, are extremely reactive acylating reagents but are, unfortunately, very sensitive to moisture and alcohols.

As polymers of intermediate reactivity that are easy to prepare and handle, we now report on the preparation of active esters of polymer-bound 4-hydroxy-3-nitrobenzophenone III (Scheme I).

Friedel–Crafts acylation is a useful modification method for polystyrene since many substituted aliphatic and aromatic acids are readily available.[8-10] In our case, the electron-withdrawing effect of the carbonyl combines with that of the nitro group to activate the substituent at the para position in I toward displacement by nucleophiles. Thus, the fluorine atom in Ia readily undergoes hydrolysis, aminolysis, and thiolysis. The methoxy group in Ic is also displaced by strong nucleophiles. Ia, Ib, and Ic all yield, upon basic hydrolysis, the desired polymeric 4-hydroxy-3-nitrobenzophenone II. It was impossible, though, to obtain II from Ic by acidic ether-cleaving reagents, such as hydriodic acid or trimethyliodosilane.

The active esters III are formed upon reaction of the polymer II with acid chlorides or anhydrides and pyridine and can thus be used effectively as acylating reagents. Comparing the relative reactivity of three relevant benzoates toward *tert*-butylamine in chloroform (see Table I), the carbonyl function provides almost a 40-fold rate increase over that of an unsubstituted *o*-nitrophenyl ester. A similar ratio is also observed for the corresponding polymers. On the other hand, the polymeric hydroxybenzotriazole esters appear to be about 100 times more reactive than the corresponding polymeric nitrophenyl esters, as opposed to a factor of 8000 for their soluble analogues. This may be attributed to a relatively slow mass transport within the polymer pores that cannot keep up with the rate of the acylation reaction. Similar effects were observed in other cases.[5,11] The polymeric active esters III have a long shelf life and are insensitive to moisture in the solvents used in their preparation and reactions.

Table I

ester			
relative acylating reactivity	1	40	8000

Since polymeric active esters are mostly used in peptide synthesis, methods for their preparation with Boc-protected amino acids were studied. The insoluble DCU precipitated inside the polymer pores when DCC was used in the usual manner. It could be washed out with a methylene chloride–methanol (2:1) mixture, but some stripping of the amino acid from the polymer by acylation of the methanol was observed. Carbodiimides that give rise to ureas that are soluble in methylene chloride and other aprotic solvents can be used.[12] A convenient and relatively fast method for the esterification involved formation of the symmetric Boc-protected amino acid anhydride with 0.5 equiv of DCC in the cold for 30 min and application of the filtered solution to the polymer with an equivalent amount of pyridine. When a 10% excess of the anhydride/pyridine mixture over the polymer was used, 70–80% of the available hydroxy groups of the polymer were found to be esterified. The loading of the polymer could be determined by its increase of weight, by titration with benzylamine, or by reaction with excess benzylamine and weighing the resulting amide. Polymeric active esters of 0.9–1.2 mmol/g were obtained with Boc-phenylalanine, Boc-glycine, and Boc-(*O*-benzyl)tyrosine.

Coupling of a C-terminal-blocked, side-chain protected free amino peptide with the polymeric active esters III to form a longer peptide was conveniently performed in chloroform with a 40% excess of the polymeric reagent, in the presence of triethylamine. The reaction was monitored by TLC with ninhydrin. Dipeptides were formed quantitatively within 10–15 min. Longer times were required as the chain length increased. No significant racemization was observed.

The use of polymeric active esters in peptide synthesis enables several coupling and deblocking cycles to be performed without isolation of intermediate peptides. The Boc-protected peptide obtained from the coupling reaction was washed successively with dilute sodium bicarbonate, cold, dilute sodium bisulfate, and water. After the solvent was dried and evaporated, trifluoroacetic acid was used for Boc deblocking. The acid was evaporated, and the peptide TFA salt reacted with the next amino acid polymeric active ester, adding 2 equiv of dry triethylamine. Thus, starting from leucine benzyl ester hydrochloride, the protected pentapeptide, Boc-Tyr(OBzl)-Gly-Gly-Phe-Leu-OBzl, showing the correct amino acid analysis, was prepared in an overall yield of 92% (crude). Work is now in progress to perform the deblocking step with suitable polymers, so

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as to achieve a continuous peptide synthesis whereby the growing peptide is the only component in solution.

The polymeric alcohol II is recyclable. A sample was subjected to three cycles of benzoylation, followed by a reaction with benzylamine for determining the amount of available OH groups, as previously described. The loading of the polymer was found to be virtually the same at each cycle.

Experimental Section

Preparation of the Polymers Ia–c. To a mixture of 50 g of macroreticular polystyrene (XE-305, Rohm & Haas) and 100 g of 4-chloro-3-nitrobenzoyl chloride was added a solution of 25 g of aluminum trichloride in 300 mL of dry nitrobenzene. The mixture was stirred mechanically at 60 °C for 5 h and poured into a mixture of 150 mL of DMF, 100 mL of concentrated HCl, and 150 g of ice. The beads slowly turned white. They were washed with 300-mL portions of DMF–water (3:1) until the washings were colorless, then with warm (60 °C) DMF, and finally with 6 portions of 300 mL of methylene chloride–methanol (2:1). The dried polymer Ib weighed 82 g (1.88 mmol/g). Anal. Calcd: N, 2.54 (1.81 mmol/g); Cl, 7.90 (2.21 mmol/g). Similarly prepared from the corresponding substituted benzoic acid chlorides were the polymers Ia and Ic, with respective loadings of 1.45 and 1.65 mmol/g.

Preparation of the Polymer II. Most experiments were carried out with polymer II prepared from Ib, due to its higher loading. Hydrolysis was carried out with a mixture of 130 mL of 40% benzyltrimethylammonium hydroxide in water, 130 mL of water, and 260 mL of dioxane, for 8 h at 90 °C. The polymer was filtered, and the process was repeated. The beads were then washed with 4 portions of warm (60 °C) dioxane. Acetic acid (30 mL) was added with stirring for 15 min. The polymer was washed with dioxane until the washings were neutral, followed by 6 portions of 300 mL of methylene chloride–methanol (2:1). Anal. Calcd: Cl, <0.1; N, 2.38 (1.7 mmol/g). The amount of available OH groups was determined by esterifing with a threefold excess of benzoyl chloride and pyridine in dry chloroform at 0–10 °C for 30 min, washing with chloroform, and reacting with excess benzylamine. The polymer was washed with chloroform, and excess benzylamine was extracted with hydrochloric acid. The organic phase afforded pure *N*-benzylbenzamide, and from its weight the loading on the polymer was determined to be 1.7–1.8 mmol/g, assuming quantitative reactions at each stage.

Preparation of Polymeric Active Esters III. Esters of simple acids were prepared from the acid chloride and pyridine as just described. Active esters of Boc-protected amino acids were prepared by the symmetric anhydride method as follows: 4 mmol of the Boc-protected amino acid was dissolved in 6 mL of methylene chloride (THF was added in cases of poor solubility). The solution was cooled to −10 to 0 °C and 2 mmol DCC was added. After 30 min at 0 °C, the mixture was filtered directly into a vessel containing 1 g of the polymer II. Pyridine (0.5 mL) was added, and the mixture was shaken for 1 h at room temperature. The polymer was washed with six to eight 10-mL portions of chloroform. Active esters of Boc-glycine, Boc-phenylalanine, and Boc-(*O*-benzyl)tyrosine were thus prepared. Determination of the loading by reacting the polymers with an excess of benzylamine and weighing the resulting amide showed that 70–80% of the available OH groups underwent esterification.

Relative Reactivity of Active Esters. *o*-Nitrophenyl benzoate, 4-(benzoyloxy)-3-nitrobenzophenone, and N^1-(benzoyloxy)benzotriazole (1 mmol each) were dissolved in 50 mL of chloroform at room temperature, and 4 mL of *tert*-butylamine was added. Disappearance times for the starting esters determined by TLC, were 11 days, 7 h, and 2 min, respectively.

Peptide Synthesis Cycle. A TFA salt of the growing peptide was dissolved in chloroform (10 mL/mmol). The polymeric active ester of the next amino acid to be coupled, in 40% excess, was added, and 2 equiv of dry triethylamine was added. Shaking was continued until complete disappearance of the spot of the starting amino peptide, determined by TLC with ninhydrin spraying. The polymer was washed with chloroform, and the combined washings were extracted with 10% sodium bicarbonate and then with cold, 10% sodium bisulfate solution. Evaporation of the solvent and Boc deblocking with trifluoroacetic acid completed the cycle. Thus, we prepared the pentapeptide Boc-Tyr(OBzl)-Gly-Gly-Phe-Leu-Obzl in an overall crude yield of 92%, starting from leucine benzyl ester hydrochloride. The peptide was hydrolyzed in 6 N HCl for 24 h and submitted to amino acid analysis. Amino acid ratios were as follows: Gly, 2.0; Phe, 0.92; Leu, 1.14; Tyr, 0.78.

Racemization Test. Starting from optically pure L-leucine methyl ester and L-phenylalanine, we prepared the dipeptide Boc-L-Phe-L-Leu-OMe as described above. Boc deblocking and reaction with benzoyl chloride resulted in formation of Bz-L-Phe-L-Leu-OMe. Any racemization in the phenylalanine during the preparation of the polymeric active ester and the coupling step would result in formation of some of the DL stereoisomer of the latter dipeptide. The diastereoisomer ratio was determined by analytical HPLC (silica column, 3% 2-propanol in hexane as eluent, UV detector set at 250 nm). The DL stereoisomer accounted for only 0.3% of the mixture.[13]

Registry No. Boc-Tyr(OBzl)-Gly-Gly-Phe-Leu-OBzl, 66831-30-9; polystyrene, 9003-53-6; 4-chloro-3-nitrobenzoyl chloride, 38818-50-7; 4-fluoro-3-nitrobenzoyl chloride, 400-94-2; 4-methoxy-3-nitrobenzoyl chloride, 10397-28-1; *N*-*tert*-butoxycarbonylglycine, 4530-20-5; *N*-*tert*-butoxycarbonylphenylalanine, 13734-34-4; *N*-*tert*-butoxycarbonyl-*O*-benzyltyrosine, 2130-96-3; *o*-nitrophenyl benzoate, 1523-12-2; 4-(benzoyloxy)-3-nitrobenzophenone, 82469-49-6; *N*-(benzoyloxy)benzotriazole, 54769-36-7; *tert*-butylamine, 75-64-9.

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(13) This test was carried out at the Department of Chemistry, University of Massachusetts, Amherst, in collaboration with Dr. L. A. Carpino.

Cyclodextrin-Mediated Chiral Sulfoxidations

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Received September 13, 1983

Sulfoxides chiral at sulfur have been used successfully to direct carbon–carbon bond formation in asymmetric syntheses;[1] furthermore, sulfoxidations mediated by flavin adenine dinucleotide monooxygenases[2a] and rat liver cytochrome P-450 isozymes[2b] occur with a stereochemical preference. While the synthesis of optically active sulfoxides is most commonly accomplished by the reaction of *O*-menthyl arene- or alkanesulfinates with Grignard reagents (Andersen synthesis),[3] the enantioselective oxidation of aryl alkyl sulfides to sulfoxides by chemical[4] and biochemical[5] methods continues to stimulate interest. Initial chemical routes using chiral oxidants (peracids, hydroperoxides) resulted in a relatively low transfer of chirality, about 8% ee at best.[6] Recently, Davis and

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