measurements (Table VI). Motion of monosaccharides in solution is generally isotropic;[47,48] that is, it is described by a single correlation time, τ_c. Furthermore, ^{13}C relaxation of protonated carbons is predominantly dipolar.[47,48] In the absence of free rotation about the C4–C5 bond, C5 will have the same correlation time as the ring carbons, and its T_1 will be half that of the ring carbons. Relaxation data in Table VI suggests that C5 has the same correlation time as the ring carbons and that motion about the C4–C5 bond is restricted, possibly through intramolecular or intermolecular (solvent) hydrogen bonding of the C5 hydroxyl group. Similar observations have been made for hydroxymethyl groups in pyranosyl rings.[40]

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Registry No. 1, 53109-84-5; 2, 85115-23-7; 3, 64609-20-7; 4, 85115-24-8; 5, 52613-15-7; 6, 25158-75-2; 7, 56607-40-0; 8, 25129-51-5; 9, 22416-73-5; 10, 52485-92-4; 11, 7473-45-2; 12, 1824-96-0; 13, 1824-97-1; 14, 85083-75-6; 15, 85083-76-7; 16, 85083-77-8; α-16, 85083-84-7; β-16, 85083-85-8; 17, 85083-78-9; α-17, 85083-88-1; β-17, 85096-82-8; 18, 85115-25-9; 19, 85083-80-3; α-19, 85083-86-9; β-19, 85083-87-0; 20, 85083-79-0; α-20, 85096-97-5; β-20, 85096-83-9; 22, 85083-81-4; 23, 85083-82-5; 24, 85083-83-6; D-erythrose, 533-49-3.

Transformation of Methionine into *S*-*tert*-Butylhomocysteine. Application to a Methionine-Containing Peptide: Substance P

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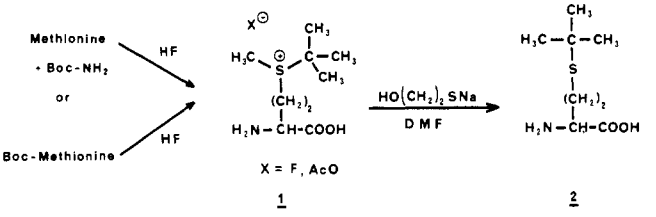
We have developed a general methodology to transform methionine into *S*-*tert*-butylhomocysteine via the *tert*-butyl sulfonium salt of methionine. This sequence of reactions can also be applied to methionine-containing peptides, as illustrated by the case of substance P (SP). Cleavage of the *S*-*tert*-butyl protecting group yields [Hcy[11]]-SP. The thiol group may undergo various reactions leading to S-modified analogues, for instance, fluorescent SP.

A large number of biologically active peptides have a methionine residue in their active core, and this amino acid is sometimes essential for the bioactivity, as for example in substance P (SP): Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2,[1] a member of the tachikinins family.[2] We have been interested in facile modification of this methionine residue either for structure–activity relationship studies or for binding studies after labeling this position with a fluorescent or a radioactive group.

A few methionine-modified analogues of eledoisin, another member of the tachikinins group, have already been described by Bernardi et al.,[3] but all these *S*-alkylhomocysteine analogues have been obtained by total synthesis. The *S*-alkylhomocysteines were synthesized via *S*-benzylhomocysteine, which was first debenzylated by sodium in liquid ammonia, yielding the thiol, which was then realkylated in situ.[4] Since we were interested in obtaining a large number of methionine-modified analogues of SP starting from the same substrate, we first considered the synthesis of [Hcy[11]]-SP using *S*-benzylhomocysteine. But deprotection by sodium in liquid ammonia of the *S*-benzyl group had to be excluded in the case of SP which contains two proline residues. Furthermore, we observed that removal of the *S*-benzyl protecting group by HF, which is used to cleave the peptide from a methylbenzhydrylamine resin (MBHA)[5] with concomitant removal of all the protecting groups, was too slow and required too long an exposure in HF, leading to many byproducts. Hence we transformed the methionine residue into *S*-*tert*-butylhomocysteine which can be used, after N-α-protection, in peptide synthesis. The *S*-*tert*-butyl group can then be easily removed.

Scheme I



Furthermore, we have established that this sequence of reactions can also be applied to peptides and thus provides a general methodology to prepare, from any methionine-containing peptide, a large variety of S-modified analogues.

Results and Discussion

S-*tert*-Butylhomocysteine (**2**) was synthesized from methionine, according to Scheme I. The use of an intermediate *S*-*tert*-butyl sulfonium salt was expected to offer two main advantages: good regioselectivity in the

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dealkylation step and easy cleavage of the *S-tert*-butyl group.

In peptide synthesis, large amounts of sulfonium salts are formed as byproducts during the removal of *tert*-butoxycarbonyl (Boc) protecting groups by HF.[6] Taking advantage of this observation and of the relative stability of these salts at low temperature and in neutral media, Bienert et al.[7] have described a quantitative conversion of SP and some other peptides into their *S-tert*-butyl sulfonium salts. They revert rapidly to the parent peptides at room temperature.

Thus, we have studied in details the formation of the *S-tert*-butylmethionine sulfonium salt in HF, either from methionine and *tert*-butyl carbamate or from (*tert*-butoxycarbonyl)methionine.[8] We have then measured the rate of attack of this sulfonium salt by different nucleophiles such as INa, INa plus 18-crown-6, N_3Na, and $HOCH_2CH_2SNa$ and found that this last reagent in dimethylformamide was the most efficient.

We established that this conversion occurs without racemization: the resulting *S-t*-BuHcy **3** was converted into Boc-Leu-(*S-t*-Bu)Hcy-NH_2 (**4**) which proved to be diastereoisomerically pure by comparison (HPLC and NMR) with dipeptide **5** obtained in the same way from racemic methionine.

We then applied this sequence directly to the peptide and synthesized [*S-t*-BuHcy^{11}]-SP from SP. This can be considered as a general method which may be applied to any methionine-containing peptide. The only limitation could be the presence in the sequence of a tryptophan residue since the indole ring can quench the *tert*-butyl cation.[9] Indeed, we verified that, under the conditions of formation of the sulfonium salt we used, free tryptophan was recovered intact.

Synthesis of *S-tert*-Butylhomocysteine (2). Neutralization of the *S-tert*-butylmethionine salt coming from HF is a crucial step for the outcome of the nucleophilic reaction. The traces of HF are rapidly eliminated, in the cold, by passage through an AG-IX-4 ion-exchange resin (acetate form), followed by two cold lyophilizations. Only sodium 2-hydroxyethyl sulfide attacks rapidly enough, compared with the rate of decomposition of the sulfonium salt, to furnish *S-tert*-butylhomocysteine (**2**) in a good yield.

Synthesis of [Hcy^{11}]-SP (7) by Solid-Phase Methodology. After N-α-protection by a *tert*-butoxycarbonyl group as described,[10] the *N*-α-Boc-*S-t*-BuHcy was introduced by solid-phase methodology as described in the Experimental Section. All the amino acids, after suitable protection, were coupled by the dicyclohexylcarbodiimide–1-hydroxybenzotriazole method except for the Boc-Gln which was introduced as the *p*-nitrophenyl ester. The *N*-α-Boc protecting groups were removed by trifluoroacetic acid–dichloromethane (1:1) without the addition of any scavenger since it is not possible to form the *S,S*-(*t*-Bu)$_2$Hcy sulfonium salt. After cleavage of the peptide from the MBHA resin and concomitant removal of the protecting groups by HF, the resultant peptide, Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Hcy-NH_2, was purified by low-pressure reverse-phase chromatography.[11] This peptide was obtained in good yields and was found homogeneous on TLC and by reverse-phase HPLC (Figure 1, supplementary material). Its structure was confirmed by alkylation of the thiol group with methyl chloride in liquid ammonia,[12] leading to substance P.

Synthesis of [*S-t*-BuHcy^{11}]-SP (9) and [Hcy^{11}]-SP (7) from SP (6). The *S-tert*-butylmethyl sulfonium salt of SP was formed in HF by starting from SP and 2 equiv of *tert*-butylcarbamate ammoniac. [*S-t*-BuHcy^{11}]-SP (**9**) was obtained in 50% yield after nucleophilic attack by the sodium 2-hydroxyethyl sulfide in dimethylformamide and purification by preparative reverse-phase HPLC. The *S-tert*-butyl group can be removed with (2-nitrophenyl)-sulfenyl chloride,[13] by mercuric acetate at pH 4,[14] by mercuric trifluoroacetate,[15] or by HF at 0 °C for 10 min to yield the [Hcy^{11}]-SP **5**.

Alkylation of [Hcy^{11}]-SP (7). The alkylation of thiols in peptides and proteins is a well-studied reaction, and different methods have already been described: (a) dimethyl sulfate in water at pH 7.5,[16] (b) methyl *p*-nitrobenzenesulfonate at pH 8.6,[17] (c) alkyl iodides in sodium–liquid ammonia,[18] and (d) alkyl chlorides in liquid ammonia.[12] In our hands, methods a and b were not very successful: the first led to many byproducts, probably due to *N*-methylation, and in the second the reagent is rapidly hydrolyzed, and a large excess is required. Finally, we found that the best method is the one described by Meienhofer et al.,[12] who had already shown its superiority over method c. Thus, we obtained substance P after alkylation of [Hcy^{11}]-SP by methyl chloride.

This method is also the most general one, and alkylation of the thiol group of [Hcy^{11}]-SP by different bifunctional alkyl chlorides is now in progress.

Synthesis of a Fluorescent SP Analogue, 10. Scouten et al.[19] reported that *N*-dansylaziridine might be used as a specific probe for the free sulhydryl group of proteins. We have observed that in 0.1 M phosphate buffer (pH 7.5) the action of *N*-dansylaziridine on [Hcy^{11}]-SP led to a complex mixture of fluorescent molecules. Such a lack of selectivity has already been reported by Sturgill et al.[20] for albumin. We found that [Hcy^{11}]-SP (**7**) reacts rapidly with *N*-dansylaziridine in liquid ammonia as described for alkyl chlorides to give only one product which has been characterized by 250-MHz ^{1}H NMR.

In conclusion, we have described a method to transform methionine into *S-tert*-butylhomocysteine. This method is general since it can be applied either to the free amino acid or to methionine-containing peptides. After removal of the *tert*-butyl protection, the thiol group may be involved in a large variety of reactions, leading to S-modified analogues.

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Experimental Section

Melting points were determined on a Kofler melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Ascending TLC on silica gel was performed on precoated silica gel plates (Merck 60, 0.25 mm thick); the spots were detected by iodine vapor or by the ninhydrin reagent. The solvent systems were (A) 4:1:5 (upper phase) 1-butanol–acetic acid–water, (B) 6:6:4.8:1.2 1-butanol–pyridine–acetic acid–water, (C) 1:9 methanol–chloroform, (D) 5:11:3 1-butanol–1% acetic acid–pyridine. High-pressure liquid chromatography (HPLC) was performed with a Waters Associate Model 204 liquid chromatography system as described,[21] and separation was accomplished on a C-18 μ-Bondapak column in the isocratic mode with the indicated percent of acetonitrile in 0.25 M triethylamine–phosphate buffer (A, pH 3.0).[22]

Preparative high-pressure liquid chromatography has been achieved with a 1 × 25 cm RP-18 Lichrosorb column in the isocratic mode at a flow rate of 1 mL/min of methanol–water–trifluoroacetic acid (50:50:0.3). ^{1}H NMR spectra were recorded on a Varian HA-100 or a Brucker 250 spectrometer. Boc-protected amino acids were purchased from Bachem. Dimethylformamide was distilled in vacuo from ninhydrin. The methylbenzhydrylamine resin was prepared according to the literature.[23]

***S*-*tert*-Butylmethionine Sulfonium Acetate 1.** This procedure is a modification of the method described by Noble et al.[6] and Bienert et al.[7] A solution of 2.49 g (1 mmol) of *N*-α-(*tert*-butoxycarbonyl)methionine in 5 mL of hydrogen fluoride was stirred at 0 °C for 10 min. After removal of HF in vacuo, the sulfonium was dissolved in 10 mL of cold water (4 °C) and stirred with 10 g of AG 1-X4A resin (CH_3COO^- form). After filtration, the resin was washed with cold water (twice), and the resulting solution (50 mL), was lyophilized at 4 °C and kept at −20 °C: ^{1}H NMR (D_2O, external Me_4Si) δ 4.2 (CH-α), 3.8 (CH_2-γ), 3.1 (CH_3S), 2.65 (CH_2β), 1.86 (*t*-BuS); ^{1}H NMR (CF_3COOD, external HMDS) δ 4.48 (CH-α), 3.44 (CH_2-γ), 2.78 (CH_3S), 2.60 (CH_2β), 1.5 (*t*-BuS).

***S*-*tert*-Butylhomocysteine Hydrochloride Salt (2).** A solution of sodium 2-hydroxyethyl sulfide (2 mmol) in DMF was added at 4 °C to a stirred solution of **1** (1 mmol) in DMF–H_2O (9:1). The mixture was stirred for 1 h at 4 °C and then acidified with acetic acid. After removal of the solvents in vacuo, the oily residue was dissolved in 2 mL of warm water and acidified with hydrochloric acid to pH 4. The resulting crystalline product was collected, washed (Et_2O), and dried to afford 2.45 g of product. The overall yield from Boc-Met was 75%: $[\alpha]^{20}_D$ +21.6° (*c* 1, 1 N HCl); TLC R_f 0.53 (A); mp 248–250 °C; ^{1}H NMR (CF_3COOD, external HMDS) δ 4.50 (CH-α), 2.84 (CH_2-γ), 2.40 (CH_2β), 1.36 (*t*-BuS).

***N*-(*tert*-Butoxycarbonyl)-*S*-*tert*-butylhomocysteine (3).** By use of method B described in the literature,[10] to 2 mmol of **2** and 4 mmol of triethylamine in 5 mL of DMF at 4 °C was added 2 mmol of di-*tert*-butyl dicarbonate. The mixture was then stirred for 2 h at room temperature. After removal of the solvent under reduced pressure the residue was dissolved in dichloromethane. The usual workup gave an oil which was further purified by column chromatography (silica gel, Et_2O) to yield **3** as an oil: 405 mg (70%). TLC R_f 0.40 (C); NMR ($CDCl_3$, Me_4Si) δ 4.3 (CH-α), 2.6 (CH_2-γ), 2.0 (CH_2β), 1.4 (N-Boc), 1.3 (*t*-BuS). The dicyclohexylamine salt of **3** was recrystallized from dichloromethane–ether: mp 138–140 °C; $[\alpha]^{20}_D$ +29.4° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{25}H_{48}N_2SO_4$: C, 63.46; H, 10.17; N, 5.93; S, 6.78. Found: C, 63.75; H, 10.17; N, 5.97; S, 6.69.

Synthesis of Boc-Leu-(*S*-*t*-Bu)Hcy-NH_2 (4) and Boc-Leu-DL-(*S*-*t*-Bu)Hcy-NH_2 (5). Boc-(*S*-*t*-Bu)Hcy-NH_2 was synthesized from **3** according to the procedure described for Boc-Met-NH_2.[24] *N*-α-Boc-Leu-OSucc (2 mmol) was coupled in CH_2Cl_2 to L-(*S*-*t*-Bu)Hcy-NH_2 (2 mmol). The resulting product was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 9.5:0.5) to yield **4**: 341 mg (42%); mp 84–86 °C; $[\alpha]^{20}_D$ −42.1° (*c* 1, $CHCl_3$); NMR ($CDCl_3$) δ 7.05 (NH of *S*-*t*-BuHcy), 6.61 (NH amide), 5.42 (NH amide), 4.88 (NH of Leu), 4.59 (CH-α of *S*-*t*-BuHcy), 4.05 (CH-α of Leu), 2.62 (CH_2-α of *S*-*t*-BuHcy), 2.08 (CH_2-β of *S*-*t*-BuHcy), 1.64 (CH_2-β and CH-γ of Leu), 1.44 (Boc), 1.31 (*t*-Bu of *S*-*t*-BuHcy), 0.94 (CH_3 of Leu); HPLC (iso, 30% CH_3CN) 24-min retention time; TLC R_f 0.70 (C). Boc-Leu-DL-(*S*-*t*-Bu)Hcy-NH_2 (**5**) was obtained by the same procedure by starting from DL-(*S*-*t*-Bu)Hcy obtained from DL-methionine, according to the above procedure. The mixture of diastereoisomers was resolved by HPLC (iso, 30% CH_3CN): 24- and 26.5-min retention times. The NMR spectrum presents a splitting of the amide resonances which is not observed with LL dipeptide **4**.

Solid-Phase Peptide Synthesis of SP 6 and [Hcy^{11}]-SP (7). Peptide syntheses were carried out manually.[25] The side chains of Arg and Lys were respectively protected by nitro (NO_2) and benzyloxycarbonyl (Cbz). Starting from a methylbenzhydrylamine resin (1 g, 0.29 mequiv/g), we coupled all the amino acids by the dicyclohexylcarbodiimide–1-hydroxybenzotriazole[26] method in DMF–dichloromethane (1:5) except for *N*-α-Boc-Gln which was coupled as its *p*-nitrophenyl ester in DMF. The coupling efficiency was monitored with the Kaiser test.[27] After removal of the last *N*-α-Boc protecting group,[6] the resins were dried in vacuo, and the protected peptide resins were treated with 1.5 mL of anisole, 0.25 mL of diethyl sulfide, and 10 mL of hydrogen fluoride per gram of peptide resin for 0.5 h at −20 °C and for 0.5 h at 0 °C. The resins were first washed with 1:1 Et_2O–$CHCl_3$, and then the peptides were eluted with 1:9 acetic acid–water. Lyophilizations of the extracts gave, respectively, 275 mg of **6** and 225 mg of **7**. SP (140 mg) was first purified by partition chromatography on Sephadex G-25-F with solvent system D to yield 67 mg of product (HPLC, minimum purity 95%) which was further purified by partition chromatography with solvent system A to yield 53 mg of SP. HPLC (iso, 24% CH_3CN) 12.0-min retention time (99% minimum purity); TLC R_f 0.19 (A), 0.49 (B); $[\alpha]^{20}_D$ −87.6° (*c* 0.5, 10% acetic acid) [lit.[24] $[\alpha]^{26}_D$ −88° (*c* 1, 5% acetic acid)]; ^{1}H NMR (D_2O, dioxane) δ 1.98 (CH_3S). The crude [Hcy^{11}]-SP from the cleavage reaction was purified by low-pressure reverse-phase liquid chromatography[11] with a linear gradient (500 mL of 1:99 trifluoroacetic acid–water, 500 mL of 1:99 trifluoroacetic acid–methanol). The crude compound (100 mg) gave 70 mg of [Hcy^{11}]-SP (HPLC minimum purity 90%). This peptide was further purified by preparative high-pressure liquid chromatography. A 10-mg injection yielded 8 mg of [Hcy^{11}]-SP (**7**): HPLC (iso, 24% CH_3CN) 14.5-min retention time (98% minimum purity); TLC R_f 0.19 (A), 0.50 (B). Amino acid analysis: Hcy, 0.54; Glu, 2.10; Gly, 1.00; Leu, 1.00; Phe, 1.94; Lys, 0.88; Pro, 1.94; Arg, 1.17. The reference used for homocystine was a sample of homocystine thiolactone which give the homocystine after treatment under the conditions of peptide hydrolysis (6 N HCl).

[*S*-*t*-BuMet^{11}]-SP (8). According to the procedure previously described for **1**, 3 mg, (2 μmol), of Substance P and 468 μg (4 μmol) of *O*-(*tert*-butyl) carbamate in 200 μL of hydrogen fluoride were stirred at 4 °C for 10 min. After removal of HF, in vacuo, and lyophilization at 4 °C **8** was used without purification.

[*S*-*t*-BuHcy^{11}]-SP (9). According to the procedure previously described for **2**, the sulfonium **8** was dissolved in 5 mL of DMF at 4 °C. After addition of a solution of sodium 2-hydroxyethyl sulfide (3 equiv) in 2 mL of DMF, the mixture was stirred, at 4 °C for 2 h. After acidification with acetic acid and removal of the solvents, in vacuo, the crude product was purified by preparative high pressure liquid chromatography (RP-18 Lichrosorb column, methanol-water-trifluoroacetic acid, 50:50:0.3) to yield 1.5 mg of **9** (50% yield): TLC R_f 0.18 (A), 0.48 (B); HPLC (iso 27% CH_3CN) 21-min retention time, 98% minimum purity; NMR (D_2O, dioxane) δ 1.08 (*t*-Bu-S), lack of δ 1.98 (CH_3S) resonance.

Alkylation of [Hcy^{11}]-SP (7). With Dimethyl Sulfate.[16] [Hcy^{11}]-SP (2 μmol) was dissolved in 200 μL of degassed phosphate buffer at pH 7.35. After addition of dimethyl sulfate (10 μmol) in 10 μL of dioxane the pH was kept at 7.5 by addition of 1 N NH_4OH. The mixture was then analyzed by HPLC (C-18 μ-

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Bondapak, triethylamine–phosphate buffer, iso 24% CH_3CN). Three peaks in the ratio 60:17:23 were observed (elution times 8.5, 10.2, and 11.5 min), the first peak corresponding to SP.

With Methyl *p*-Nitrobenzenesulfonate.[17] To [Hcy[11]]-SP (2 μmol) in 1 mL of 0.1 M Tris buffer (pH 8.6) was added dropwise under N_2 stream 300 μmol of methyl *p*-nitrobenzenesulfonate in 300 μL of CH_3CN. The mixture was then analyzed by HPLC (C-18, μ-Bondapak, triethylamine–phosphate buffer, iso 24% CH_3CN). SP and [Hcy[11]]-SP in the ratio 20:80 were observed.

With Chloromethane.[12] To a stirred solution of [Hcy[11]]-SP (2 μmol) in 10 mL of dry liquid ammonia, protected from moisture and CO_2, was introduced a large excess of CH_3Cl gas, and the mixture was stirred for 10 min. After evaporation of the liquid ammonia and lyophilization the product was purified by preparative high-pressure liquid chromatography (RP-18 Lichrosorb column, 50:50:0.3 methanol–water–trifluoroacetic acid). Only one peak, corresponding to SP, was observed, the recuperation yield being 50%.

[*S*-[2-(Dansylamino)ethyl]-Hcy[11]]-SP (10) as Described by Scouten.[19] [Hcy[11]]-SP (2 μmol) and *N*-dansylaziridine (20 μmol) in 200 μL of 0.1 M phosphate buffer (pH 7.5) were stirred at room temperature. The evolution of the reaction was monitored by TLC (solvent system A). This method gave a complex mixture which was not further analyzed.

In Dry Liquid Ammonia. This procedure was done according to the previously described procedure for the alkylation of **7** with chloromethane, 5 μmol of **7** in 10 mL of dry liquid ammonia, and 20 μmol of *N*-dansylaziridine. After dissolution of the residue in 10% acetic acid and lyophilization, the product was purified by preparative HPLC (RP-18 Lichrosorb column, 50:50:0.3 methanol–water–trifluoroacetic acid) to yield **10**: 5 mg (56%); TLC R_f 0.19 (A); HPLC (iso, 30% CH_3CN) 13-min retention time (97% minimum purity); ^1H NMR (D_2O, dioxane, pH 4.5) from the dansyl group δ 8.66 (d), 8.18 (d) 8.12 (d), 7.53 (t), 7.52 (t), 7.30 (d), 2.92 ($SCH_2CH_2NHSO_2$), 2.75 ($(CH_3)_2N$), 2.27 ($SCH_2CH_2NHSO_2$). The other resonances are identical with those of SP.

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Registry No. 1, 85097-56-9; **2**, 85097-57-0; **3**, 85097-58-1; **4**, 85097-59-2; **5**, 85097-60-5; **6**, 33507-63-0; **7**, 85115-64-6; **8**, 85115-65-7; **9**, 85115-66-8; **10**, 85115-67-9; *N*-α-(*tert*-butoxycarbonyl)methionine, 2488-15-5; di-*tert*-butyl dicarbonate, 24424-99-5; *N*-α-Boc-Leu-OSucc, 3392-09-4; L-(*S*-*t*-Bu)Hcy-NH_2, 85097-61-6; DL-(*S*-*t*-Bu)Hcy, 85097-62-7; L-methionine, 63-68-3; *S*-*tert*-butylhomocysteine, 62965-24-6.

Supplementary Material Available: Figure 1, containing HPLC traces of [Hcy[11]]-SP (1 page). Ordering information is given on any current masthead page.

Notes

Oxidation of Tertiary Phosphines and Arsines with Sulfur Trioxide and Sulfuryl Chloride Fluoride: Demonstration of Ambident Reactivity[1]

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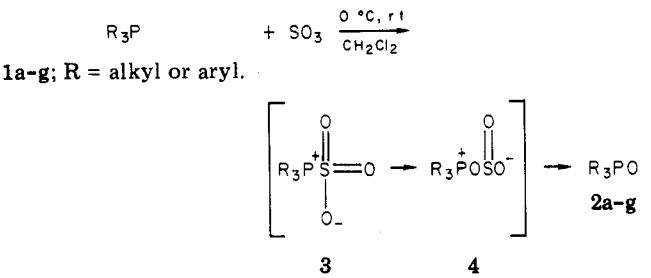
The ambident reactivity of certain nucleophiles is well established. Nitrite ion (NO_2^-), cyanide ion (CN^-), and enolates of carbonyl compounds are well-known ambident nucleophiles.[4] However, the ambident behavior of electrophiles is in general limited to allyl cations and other resonance-stabilized cations.[4] Recently, we reported[5] the ambident reactivity of the nitronium ion (NO_2^+) toward sulfides, selenides, and phosphines, resulting in the oxidation of these substrates. Considering similarities in reactivity between the nitronium ion and sulfur trioxide in electrophilic aromatic substitution reactions, we thought it of interest to extend our studies to the possible ambident reactivity of sulfur trioxide.

Although sulfur trioxide is known as a strong oxidant, the mechanism of such reactions is not yet fully understood and generally is considered to be due to radical processes. It has been, for example, reported that SO_3 when reacted with methane at elevated temperatures (100–450 °C) and pressure (70 atm) gives a mixture of sulfonated and oxygenated products.[6-8] Other hydrocarbons also show similar behavior. The mechanism of the reaction was not established, but the forcing reaction conditions could indicate free-radical oxidation. Representative example of oxidation of halohydrocarbons with SO_3 are that of pentachlorotoluene to pentachlorobenzyl alcohol and pentachlorobenzaldehyde[9] and of trichlorofluoromethane and tribromofluoromethane to carbonyl chloride fluoride and carbonyl bromide fluoride,[10] respectively.

Scheme I



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