pendent reflections for $\theta < 57$, 1459 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[13] and was refined by full matrix least squares to $R = 0.046$ and $R_w = 0.067$ (heavier atoms anisotropic, hydrogen atoms isotropic and not refined). The final difference map has no peaks greater than ±0.3 eA^{-3}.

Registry No.—**1b**, (R = H), 56377-67-4; **1b** (R = Et), 56377-68-5.

Supplementary Material Available: Tables III, IV, and V listing bond distances, bond angles, and torsion angles of compound **1b** (R = Et) (3 pages). Ordering information is given on any current masthead page.

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Benzamidomethyl Group as a Thiol Protecting Group for Cysteine, *N*-Methylcysteine, and Corresponding *N-tert*-Butyloxycarbonyl Derivatives

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New protecting groups for the thiol function of cysteine are of current interest.[1] The acetamidomethyl (Acm) group[2] has been reported for use with cysteine in peptide synthesis. In our laboratory, attempted use of the Acm group for protection of the thiol function in *N*-methyl-L-cysteine[3] gave noncrystalline material that was shown by TLC analysis to be a mixture of products. We therefore investigated use of the related benzamidomethyl (Bam) group and report this group to be a convenient thiol protective group for cysteine and *N*-methylcysteine.

The benzamidomethyl group was conveniently incorporated into L-cysteine and *N*-methyl-L-cysteine by treatment of equimolar ratios of *N*-hydroxymethylbenzamide[4] and the respective amino acid in anhydrous trifluoroacetic acid (F_3AcOH) at room temperature. Upon removal of F_3AcOH under reduced pressure, the S-protected derivatives **1** and **2** were isolated in good yield as the trifluoroacetate salts. By analogy with the procedure for introduction of the *S*-trityl group,[5] we have found the use of F_3AcOH as solvent and acid catalyst to be effective and convenient.

$$Cl^-H_2^+\text{-Cys-OH} + C_6H_5CONHCH_2OH \rightarrow \underset{1}{F_3AcO^-\ H_2^+\text{-Cys(Bam)-OH}}$$

$$\text{H-MeCys-OH} + C_6H_5CONHCH_2OH \rightarrow \underset{2}{F_3AcO^-\ H_2^+\text{-MeCys(Bam)-OH}}$$

The *S*-benzamidomethyl group was found to be stable to a wide variety of reaction conditions commonly used in peptide synthesis (Table I). Removal of the Bam group was effected by treatment at pH 4 and room temperature with 2 equiv of Hg(II).

Table I. Studies on Stability of Bam Group to Various Deblocking Conditions

Reagents–solvents–temp	Reaction time (h)	Stability of Bam group
1 N NaOH–H_2O–25 °C	5	Stable
1 N HCl–H_2O–25 °C	5	Stable
6 N HCl–H_2O–110 °C	24	Not stable
N_2H_4·H_2O–MeOH–25 °C	24	Stable
Zn–90% AcOH–0 °C	5	Stable
Anhydrous F_3AcOH–25 °C	5	Stable

The *N-tert*-butyloxycarbonyl (Boc) derivatives **3** and **4** were prepared in good yield by treatment of the respective S-protected derivatives **1** and **2** with 2 equiv of *tert*-butylazidoformate[6] in the presence of tetramethylguanidine. The Boc derivative **4** was isolated as the crystalline dicyclohexylammonium salt. Compound **3** was converted into the *N*-hydroxysuccinimido active ester **5** by reaction with *N,N'*-dicyclohexylcarbodiimide and *N*-hydroxysuccinimide.[7]

Boc-Cys(Bam)-OR

3, R = H

5, R = NSu

$$\text{Boc-MeCys(Bam)-O}^-\ H_2N^+(C_6H_{11})_2$$

4

Experimental Section

Melting points are uncorrected. TLC analysis was carried out on silica gel plates (Quanta gram) in the following solvent systems: A, *n*-BuOH–AcOH–H_2O (10:2:3); B, $CHCl_3$–95% EtOH (8:2). Spots were located by ninhydrin spray, iodine, and ultraviolet light. NMR spectra were recorded on a Varian EM360 spectrometer using Me_4Si as an internal standard.

***S*-Benzamidomethyl-L-cysteine Trifluoroacetate (1).** A mixture of L-cysteine hydrochloride (3.61 g, 10.0 mmol) and *N*-hydroxymethylbenzamide[4] (4.53 g, 10.0 mmol) in anhydrous F_3AcOH (30 mL) was stirred at room temperature for 45 min. The solvent was removed in vacuo, the residue was dissolved in absolute ethanol (30 mL), and the solution was evaporated to dryness in vacuo. This process was repeated twice, and the residue obtained was triturated with ether, filtered, washed with ether, and dried under vacuum over NaOH and P_2O_5. The product[8] was recrystallized from 95% ethanol to yield 6.6 g (60%) of **1**: mp 169–171 °C; $[\alpha]^{25}_D$ −33.3° (*c* 1.0, H_2O); R_f 0.32 (A); NMR (Me_2SO-d_6) δ 3.45 (m, 2 H, Cys methylene), 4.24 (m, 1 H, α-H), 4.77 (d, 2 H, Bam methylene), 7.50–8.80 (m, 9 H, aromatic and NH).

Anal.[9] Calcd for $C_{11}H_{14}N_2O_3S$·CF_3COOH: C, 42.39; H, 4.08; N, 7.61. Found: C, 42.43; H, 4.14; N, 7.53.

***S*-Benzamidomethyl-*N*-methyl-L-cysteine Trifluoroacetate (2).** *N*-Methyl-L-cysteine (5.0 g, 37 mmol) and benzamidomethanol (5.6 g, 37 mmol) in anhydrous F_3AcOH (50 mL) was treated as described above for **1**. The crude product[8] (mp 166–168 °C) was recrystalized from 95% ethanol to yield 12.5 g (88%) of **2**: mp 169–170 °C; $[\alpha]^{25}_D$ +34.5° (*c* 1, H_2O); R_f 0.29 (A); NMR (Me_2SO-d_6) δ 2.60 (s, 3 *H*, *N*-methyl), 3.27 (m, 2 H, Cys methylene), 4.27 (m, 1 H, α-H), 4.50

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(m, 2 H, Bam methylene), 7.10–8.30 (m, 9 H, aromatic plus exchangeable protons).

Anal.[9] Calcd for $C_{12}H_{16}N_2O_3S \cdot CF_3COOH$: C, 43.97; H, 4.45; N, 7.32. Found: C, 44.05; H, 4.61; N, 7.52.

***N*-*tert*-Butyloxycarbonyl-*S*-benzamidomethyl-L-cysteine (3).** A mixture of 1 (4.10 g, 11.1 mmol) and tetramethylguanidine (2.39 g, 22.3 mmol) in 30 mL of anhydrous dimethylformamide was stirred in an ice bath. To the cold reaction mixture was added dropwise and simultaneously *tert*-butyloxycarbonyl azide[6] (2.90 g, 22.3 mmol) and tetramethylguanidine (2.39 g, 22.3 mmol). The mixture was stirred at room temperature for 48 h, and the solvent was removed in vacuo. The residue was dissolved in water (60 mL) and extracted with ether (2 × 20 mL), and the aqueous phase was acidified, with cooling, by the addition of solid citric acid. The oil that separated was extracted with ethyl acetate (100 mL), and the organic phase was washed with water and dried over anhydrous $MgSO_4$. Upon removal of solvent, the product was obtained as a viscous oil that crystallized from ether: 3.75 g (95%); mp 141–142 °C; $[\alpha]^{25}_D$ −28.5° (*c* 1, methanol); R_f 0.8 (A); NMR ($CDCl_3$–Me_2SO-d_6, 5:1) δ 1.46 (s, 9 H, *t*-Bu), 3.16 (m, 2 H, Cys methylene), 4.30–4.80 (m, 3 H, Bam methylene and α-H), 6.40 (m, 1 H, NH), 7.35–8.32 (m, 6 H, aromatic and NH), 8.90 (m, 1 H, carboxyl hydrogen).

Anal. Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.24; H, 6.22; N, 7.70. Found: C, 54.12; H, 6.34; N, 7.56.

***N*-*tert*-Butyloxycarbonyl-*N*-methyl-*S*-benzamidomethyl-L-cysteine Dicyclohexylammonium Salt (4).** Compound 4 was prepared by treatment of a mixture of **2** (12.3 g, 32.2 mmol) and tetramethylguanidine (6.88 g, 64.4 mmol) in 80 mL of dry dimethylformamide with *tert*-butyloxycarbonyl azide (8.36 g, 64.4 mmol) and tetramethylguanidine (6.88 g, 64.4 mmol) as described above for the preparation of **3**. The product **4** was isolated as an oil, which was taken up in cold ether and treated with dicyclohexylamine (5.98 g). The dicyclohexylammonium salt, which crystallized, was collected by filtration, washed with ether (15 mL), and dried to yield 17.2 g (97%) of **4**: mp 147–148 °C; $[\alpha]^{25}_D$ −95° (*c* 1, methanol); R_f 0.77 (A) 0.57 (B); NMR ($CDCl_3$) δ 0.9–2.1 (br m, 31 H, *t*-Bu and cyclohexyl), 2.9 (m, 5 H, *N*-methyl and Cys methylene), 4.3–4.9 (m, 3 H, Bam methylene and α-H), 7.4–8.2 (m, 6 H, aromatic and NH), 8.5–8.9 (br m, 2 H, ammonium NH).

Anal. Calcd for $C_{17}H_{24}N_2O_5S \cdot C_{12}H_{23}N$: C, 63.38; H, 8.56; N, 7.65. Found: C, 63.52; H, 8.66; N, 7.81.

***N*-*tert*-Butyloxycarbonyl-*S*-benzamidomethyl-L-cysteine *N*-Hydroxysuccinimide Ester (5).** A mixture of **3** (1.05 g, 3.0 mmol), *N*-hydroxysuccinimide (0.36 g, 3.0 mmol), and *N,N'*-dicyclohexylcarbodiimide (0.63 g, 3.0 mmol) in dry tetrahydrofuran (10 mL) was stirred at 0 °C for 2 h and then allowed to stand overnight in a refrigerator. The dicyclohexylurea was removed by filtration and the solvent removed in vacuo. The residue was taken up in ethyl acetate (30 mL), washed with 10% $NaHCO_3$ and water, and dried over $MgSO_4$. Removal of the solvent in vacuo gave an amorphous solid that was crystallized from 2-propanol to yield 0.97 g (72%) of ester **5**: mp 145–146 °C; $[\alpha]^{25}_D$ −117.5° (*c* 1, chloroform); R_f 0.86 (A); NMR ($CDCl_3$) δ 1.49 (s, 9 H, *t*-Bu), 2.90 (s, 4 H, succinimido protons), 3.30 (m, 2 H, Cys methylene), 4.83 (m, 3 H, Bam methylene and α-H), 5.78 (m, 1 H, NH), 7.33–8.28 (m, 6 H, aromatic and NH).

Anal. Calcd for $C_{20}H_{25}N_3O_7S$: C, 53.22; H, 5.54; N, 9.31. Found: C, 53.11; H, 5.64; N, 9.41.

Removal of the *S*-Benzamidomethyl Group. Compound 1 (37 mg, 0.1 mmol) was dissolved by warming in 5 mL of methanol–water (1:1). The clear solution was treated at room temperature with mercuric acetate (32 mg, 0.1 mmol) and the mixture was stirred for 1 h. Hydrogen sulfide was passed into the reaction mixture for 10 min and the precipitate was removed by filtration. TLC analysis (solvent A) showed that complete deblocking of 1 had occurred and that the product formed was cysteine as shown by comparison with an authentic sample.

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Registry No.—1, 64840-21-7; **2**, 64840-23-9; **3**, 33375-72-3; **4**, 64840-25-1; 4 free acid, 64840-24-0; **5**, 64852-94-4; L-cysteine hydrochloride, 52-89-1; *N*-hydroxymethylbenzamide, 6282-02-6; *N*-methyl-L-cysteine, 4026-48-6; *tert*-butyloxycarbonylazide, 1070-19-5; dicyclohexylamine, 101-83-7; *N*-hydroxysuccinimide, 6066-82-6.

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(8) The crude product was found to be reasonably pure and could be used to prepare the corresponding Boc derivatives without further purification.
(9) The analytical sample was prepared by recrystallization of 0.5 g of crystalline product from a minimum volume of water.

Reaction of Singlet Oxygen with Nitronate Salts, Conversion of Nitro Compounds into Carbonyls

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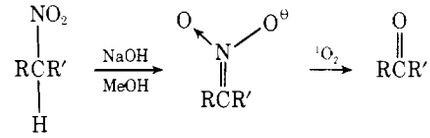
Methods for the conversion of nitro compounds to carbonyls have recently been summarized by McMurray and co-workers.[1] These workers reported that the ozonolysis of nitronate salts produces aldehydes and ketones in good yields. Unfortunately, this method uses ozone, which can react with other functional groups in a substrate, and also involves a relatively long workup procedure. Since singlet oxygen, like ozone, is an electrophilic species, it should also react very rapidly with nitronate results, but may react differently with the rest of the molecule. For example, ozone will react with a monosubstituted olefin,[2] whereas it is inert to singlet oxygen.[3]



Reaction of the nitronate salt with singlet oxygen, generated in situ using dye-sensitized photooxygenation, afforded the corresponding carbonyl compound rapidly and in good yield. Some of our results are given in Table I. When the nitronate salt of 5-nitro-1-hexene was treated with this procedure, 5-keto-1-hexene was obtained, whereas using ozone a ketoozonide would have been produced. To confirm that singlet oxygen was indeed the reactive species involved, 1,4-diazabicyclo[2.2.2]octane (Dabco), a known singlet oxygen quencher, was added.[4] In all cases there was no formation of ketone, indicating Dabco had quenched all the singlet oxygen produced.

In summary, singlet oxygen provides a more facile alternative procedure to the use of ozone for the preparation of carbonyl compounds from nitronate salts. Recently, a very convenient dry method was reported for the conversion of nitro groups into carbonyls.[5]

Experimental Section

General Reaction Procedure. A water-cooled immersion irradiation apparatus similar to the one described by Gollnick and Schenck was used.[6] O_2 was recirculated by a Cole–Parmer Masterflex Tubing Pump. The solutions were irradiated with a Sylvania Q/CL 500-W tungsten–halogen lamp operating at 110 V for 1 h. Oxygen uptake was measured by a gas burette.

The nitro compound (5.0 mM) in 10 mL of methanol with 1 mg of rose bengal added was treated with 1.1 equiv of NaOH (0.55 mL, 10 N) to form the nitronate salt. The solution was then cooled to 0 °C

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