Oxidations of 5 in H_2O. The purification of **5** and the glassware for two parallel reactions in the same oil bath above a single magnetic stirring motor have been described.[1c] To one flask were added 0.499 g (3.33 mmol) of **5** and 66.0 mg (0.152 mmol) of **1b**, and to the other, 0.499 g of **5**, followed by the addition of 12.5 mL of H_2O to each. To each stirred system at 50–60 °C was added, during 15 min, a solution of 0.75 g (4.7 mmol) of $KMnO_4$ in 17.5 mL of H_2O. The reaction mixtures then were stirred for 150 min at 50–60 °C and worked up with the published procedure[1c] on one-half scale. For the system with **1b**, foaming was observed before the addition of $KMnO_4$ and during the wash of MnO_2. Thereafter, there was no evidence of foaming or emulsion formation beyond that in the other reaction. From the reaction with **1b**, 0.247 g (45%) of **6**, mp 229–230 °C (lit.[13] mp 230–232 °C), was obtained, and from the other, 0.164 g (30%) of **6**, mp 227–230 °C. A second reaction with **1b** identical with that above gave a 44% yield of **6**: mp 229–230 °C. In this reaction, the pH of the reaction mixture was 7 before and during the addition of the $KMnO_4$ solution and throughout the 150-min period.

Oxidations of 5 in H_2O–C_6H_6. Individual reactions were performed in glassware previously described,[1c] in an oil bath held at 50–55 °C. To the flask were added 1.00 g (6.67 mmol) of **5**, 0.131 g (0.302 mmol) of **1b**, 25 mL of H_2O, and 50 mL of C_6H_6. After a solution of 1.5 g (9.5 mmol) of $KMnO_4$ in 35 mL of H_2O was added during 30 min, the reaction mixture was stirred for an additional 150 min and filtered. The aqueous portion of the filtrate was pH 8, and the MnO_2 was washed with 50 mL of H_2O (60 °C) and 20 mL of C_6H_6. The combined filtrates were shaken vigorously to give an emulsion that persisted for 5 min. Then 0.76 mL of 1.0 M *n*-Bu_4NF (0.76 mmol) in THF was added, and the mixture was shaken vigorously for 20 min. The aqueous layer was acidified with 10% hydrochloric acid, and the resultant precipitate was collected, washed with H_2O, and dried to give 0.718 g (65%) of **6**: mp 229–230 °C. The C_6H_6 layer was dried ($MgSO_4$) and rotary evaporated to give 0.25 g of an oil, which by ^1H NMR contained predominantly **2** and **5**. An identical reaction gave 0.681 g (61%) of **6** with the same melting point.

The above procedure with the substitution of 0.110 g (0.302 mmol) of HTABr for **1b** was used for two reactions, which gave 0.623 g (56%) and 0.597 g (54%) of **6**: mp 229–230 °C. In these reactions, vigorous shaking of the combined filtrates gave an emulsion that persisted for 2–3 h. For two reactions without surfactant, the above procedure gave 0.146 g (13%) and 0.129 g (12%) of **6**: mp 229–230 °C.

Acknowledgment is made to the U.S. Army Research Office, to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Marathon Oil Co. for support of this research.

Registry No. **1a**, 81372-17-0; **1b**, 81372-19-2; **1c**, 81372-20-5; **2**, 81372-22-7; **3** (X = Cl), 67-48-1; **5**, 120-57-0; **6**, 94-53-1; Me_3CLi, 594-19-4; $AgNO_3$, 7761-88-8; $NaBPh_4$, 143-66-8; $C_{12}H_{25}(CMe_3)SiCl_2$, 18407-07-3; $C_{12}H_{25}(Me)Si(CMe_3)Cl$, 81372-21-6.

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A Convenient and Highly Chemoselective Method for the Reductive Acetylation of Azides

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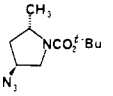
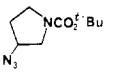
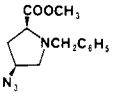
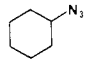
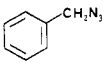
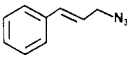
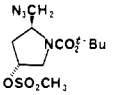
Received October 9, 1987

Results and Discussion

The reduction of azides to amines is an important and widely used reaction in organic synthesis.[1] It is especially useful because of the ease of synthesis and high stereoselectivity associated with the preparation of the precursor azides. Thus, the reduction represents a pivotal step in a stereoselective sequence for the preparation of amines. Several methods and reagents are available for this transformation that is often carried out by catalytic hydrogenation[2,7] or by treatment with lithium aluminum hydride.[3] Other known procedures include H_2S/pyridine/H_2O,[4] transfer hydrogenation,[5] Ph_3P,[6] H_2/Lindlar catalyst,[7] $Cr(II)/H^+$,[8] and $Na_2S/Et_3N/MeOH$.[9] Most recently, there have been reports utilizing stannous chloride/MeOH[10] and $NaBH_4$/THF/MeOH.[11] The large number of reagents that have been employed to achieve this transformation is related to a lack of chemoselectivity or relatively vigorous conditions often associated with some of these methods.

In this paper, we report a convenient and highly chemoselective reduction of azides that occurs with concomitant acetylation to give the corresponding acetamide (eq

Table I. Reductive Acylation of Azides with Thioacetic Acid

	azide (1)[13]	% yield of acetamide (2)	mp (lit. mp), °C
(a)		84	108–110
(b)		77	oil
(c)		92	62–64
(d)	$CH_3(CH_2)_6N_3$	77	oil
(e)		65	104 (104)[14]
(f)		91	58–60 (60)[14]
(g)		73	88–90
(h)		70	oil

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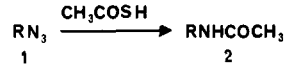
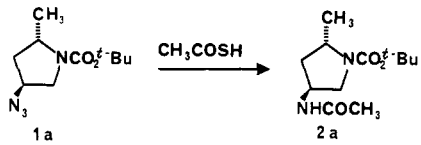
1). Treatment of the enantiomerically homogeneous azide



(eq 1)

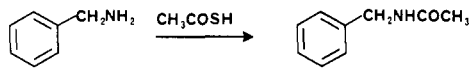
1a with thioacetic acid at room temperature results in the smooth conversion to **2a**.[12] The material obtained in this



reductive acetylation is identical with that afforded upon sequential treatment of **1a** with hydrogen/Pd–C and acetic anhydride. In order to evaluate the selectivity and general utility of this reagent, we examined the reduction of several functionally diverse azides. The results are shown in Table I. All of the yields represent isolated pure products. It can be seen that several functional groups that are labile to various alternative methods are stable to the conditions required by using this protocol. They include *tert*-butoxycarbonyl (**1a,b,h**) and benzyl (**1c**) protecting groups, a methyl ester (**1c**), an olefin (**1g**), and the methanesulfonate ester **1h**.

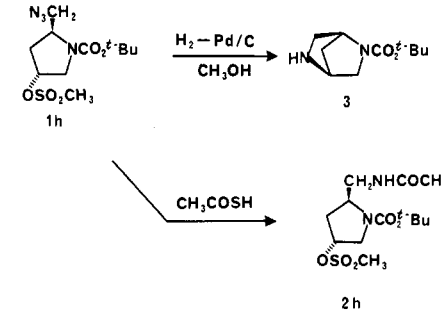
The reaction is convenient to carry out and involves simply stirring the azide with 4 to 10 molar equiv of thioacetic acid and then concentrating the reaction mixture with a rotary evaporator (bp of thioacetic acid: 88–91.5 °C). The reaction is often complete within a matter of minutes.

As part of our effort to better understand the mechanism of this reaction, we subjected benzylamine to the conditions of this method, resulting in a rapid and virtually quantitative conversion to the corresponding acetamide (eq 2). There has been a report in the literature that



(eq 2)

thioacetic acid acetylates aromatic amines.[15] The observed rapid acetylation of benzylamine under the conditions required for azide reduction suggested that the scope of this method might be broadened to include substrates that possess functional groups that are incompatible with a free amine, that is, perhaps acetylation occurs so rapidly under these conditions that an incipient amine derived from the reduction process might be trapped before reacting with another functional group either by an intermolecular or an intramolecular process. Thus, we examined the reduction of the azido mesylate **1h**. Exposure of **1h** to hydrogen and a palladium catalyst resulted in reduction of the azide and subsequent cyclization to the bicyclic amine **3** in quantitative yield. The cyclization occurred



spontaneously under the conditions of the reaction (RT, MeOH, 1 h), and no amino mesylate was obtained. However, treatment of **1h** with thioacetic acid affords cleanly the acetamido mesylate **2h**, in which the amine is acylated prior to the intramolecular displacement reaction.

The observed reaction may be initiated by traces of H_2S that are present in thioacetic acid, as H_2S is known[4] to reduce azides. The subsequent acetylation would then generate a molar equivalent of H_2S.[15] Alternatively, the thioacetic acid may actually be acting as a reducing agent. We are currently investigating these alternatives. Presently, this method should be of general utility for the reduction of azides, particularly those possessing functional groups incompatible with amines. The conditions are quite mild, the reagent is highly chemoselective, and from a practical standpoint the method is quite convenient to carry out. We are also studying the extension of this reaction to the production of amines protected with alternative groups.

Experimental Section

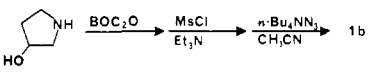
Procedures for the reductive acetylation of **1a** and benzyl azide are provided and are representative of the general procedure employed. Spectral and physical data are also provided for **2c** and **2h**, which have not been described previously.

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Melting points are uncorrected. ^1H NMR spectra were determined on a General Electric GN-300 spectrometer operating at 300.1 MHz. NMR spectra were determined with $CDCl_3$ as the solvent, unless otherwise noted. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the order multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectra were obtained with a Hewlitt-Packard 5985A mass spectrometer. Flash column chromatography[16] was done with Matrex silica gel (particle size, 35–70 μM). Elemental analyses were performed by the Microanalytical Laboratory, operated by the Analytical Department, Abbott Laboratories, North Chicago, IL.

(2*S*,4*S*)-4-Acetamido-1-(*tert*-butoxycarbonyl)-2-methylpyrrolidine (2a). Under a nitrogen atmosphere in a 25-mL round-bottom flask equipped with a rubber septum and a magnetic stir bar was placed 210 mg (0.93 mmol) of azide **1a**. To the system was added 0.27 mL (280 mg, 3.7 mmol) of thioacetic acid. The reaction mixture was stirred at room temperature for 4 h and concentrated with a rotary evaporator. The resulting oil was subjected to flash column chromatography (50 g of silica gel) using 1:1 ethyl acetate/hexane followed by ethyl acetate as the eluant to obtain 190 mg (84% yield) of the acetamide **2a** as a yellow oil which solidified on standing. Recrystallization of a small sample from hexanes provided a white solid. The material thus obtained was identical in all respects with that obtained by sequential hydrogenation and acetylation (Ac_2O) of **1a**: mp 108–110 °C; ^1H NMR δ 1.23 (d, 3 H, J = 6.2), 1.46 (s, 9 H), 1.71 (s, 1 H), 1.98 (s, 3 H), 3.23 (br, 2 H), 3.63 (br, 1 H), 3.94 (br, 1 H), 4.50 (dd, 1 H, J = 6.4, 12.7), 5.61 (br, 1 H); mass spectrum, m/z 243 (parent + H), 204, 187, 143. Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H,

(12) For details of the synthesis of **1a**, see: Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Shen, L.; Pernet, A. G. *International Telesymposia Proceedings on Quinolones*, in press.

(13) Preparation of azides: **1a**, ref 12; **1b**,



1c, Rosen, T.; Fesik, S. W.; Chu, D. T. W.; Pernet, A. G. *Synthesis*, in press; **1d–g**, treatment of corresponding commercially available bromide with n-Bu_4NN_3; **1h**, ref 12.

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9.15; N, 11.56. Found: C, 59.15; H, 9.20; N, 11.29.

Benzylacetamide (2f). Under a nitrogen atmosphere in a 50-mL round-bottom flask equipped with a magnetic stir bar and a rubber septum was placed 570 mg (4.3 mmol) of benzyl azide. To the system was added 1.2 mL (1.3 g, 17.2 mmol) of thioacetic acid. This solution was stirred at room temperature for 1 h, and the thioacetic acid was removed with a rotary evaporator. The resulting oil was subjected to flash column chromatography (50 g of silica gel) using 1:1 ether/pentane followed by ether as the eluant to obtain 580 mg (91% yield) of benzylacetamide as a white crystalline solid, mp 58–60 °C.

Reaction of Benzylamine with Thioacetic Acid. Under a nitrogen atmosphere in a 50-mL round-bottom flask equipped with a magnetic stir bar and a rubber septum was placed 0.54 mL (535 mg, 5 mmol) of benzylamine. To the system was added 1.4 mL (1.5 g, 20 mmol) of thioacetic acid, upon which a precipitate formed instantaneously. The thioacetic acid was removed with a rotary evaporator to obtain 740 mg (quantitative yield) of benzylacetamide as a yellow solid. Recrystallization from hexanes afforded 690 mg (92% yield) of pure benzylacetamide. The physical and spectral properties of the material obtained in this manner were identical with those of the product obtained upon treatment of benzylazide with thioacetic acid.

(2*R*,4*S*)-4-Acetamido-1-benzyl-2-carbomethoxypyrrolidine (2c): mp 62–64 °C; ^{1}H NMR δ 1.92 (s, 3 H), 1.96 (dd, 1 H, J = 2.6, 7.7), 2.4 (m, 2 H), 3.35 (dd, 1 H, J = 6.6, 9.6), 3.56 (dd, 1 H, J = 5.7, 8.6), 3.67 (d, 1 H, J = 12.9), 3.69 (s, 3 H), 3.86 (d, 1 H, J = 13.2), 4.51 (br, d, NH, J = 6.6), 5.51 (m, 1 H), 7.27 (m, 5 H); mass spectrum, m/z 277 (parent + H). Anal. Calcd for $C_{15}H_{20}N_2O_3 \cdot {}^2/_3H_2O$: C, 62.47; H, 7.45; N, 9.71. Found: C, 62.60; H, 7.27; N, 9.71.

(2*S*,4*R*)-2-(Acetamidomethyl)-1-(*tert*-butoxycarbonyl)-4-[(methylsulfonyl)oxy]pyrrolidine (2h): ^{1}H NMR δ 1.49 (s, 9 H), 1.99 (s, 3 H), 2.42 (ddt, 1 H, J = 2.3, 7.5, 14.3), 3.04 (s, 3 H), 3.20 (br, 1 H), 3.55 (br, 2 H), 3.91 (br, d, 1 H, J = 13.2), 4.10 (d, 1 H, J = 7.0), 4.14 (d, 1 H, J = 7.0), 5.16 (m, 1 H), 5.90 (br, NH); mass spectrum, m/z 337 (parent + H), 298, 281, 237. Anal. Calcd for $C_{13}H_{24}N_2O_6S \cdot {}^2/_3H_2O$: C, 44.83; H, 7.27; N, 8.04. Found: C, 45.01; H, 7.20; N, 7.64.

Registry No. **1a**, 113451-51-7; **1b**, 113451-52-8; **1c**, 113451-53-9; **1d**, 44961-22-0; **1e**, 19573-22-9; **1f**, 622-79-7; **1g**, 57294-86-7; **1h**, 113451-54-0; **2a**, 113451-55-1; **2b**, 113451-56-2; **2c**, 113451-57-3; **2d**, 14202-55-2; **2e**, 1124-46-5; **2f**, 588-46-5; **2g**, 6158-94-7; **2h**, 113451-58-4; **3**, 113451-59-5; HSAc, 507-09-5; $PhCH_2NH_2$, 100-46-9.

Thioaldehyde Anion Radicals

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Whereas the radical anions of aldehydes have long been known and extensively investigated by ESR spectroscopy,[1,2] the radical anions of the corresponding thioaldehydes had not been directly detected. On the other hand, a large amount of information is available on the radical anions of thioketones,[3-8] allowing the comparison of their spectral properties with those of the corresponding ketyl radicals. The absence of examples of thioaldehyde radical anions is due to the fact that the parent molecules, contrary to thioketones, are too unstable to be isolated.[9] As a consequence, the reactions employed to produce the radical anions from thioketones could not be applied to thioaldehydes.

It is known, however, that the benzaldehyde radical anion **1** can be obtained by radiolysis of benzyl alcohol in aqueous alkaline solutions.[10] We observed that the same

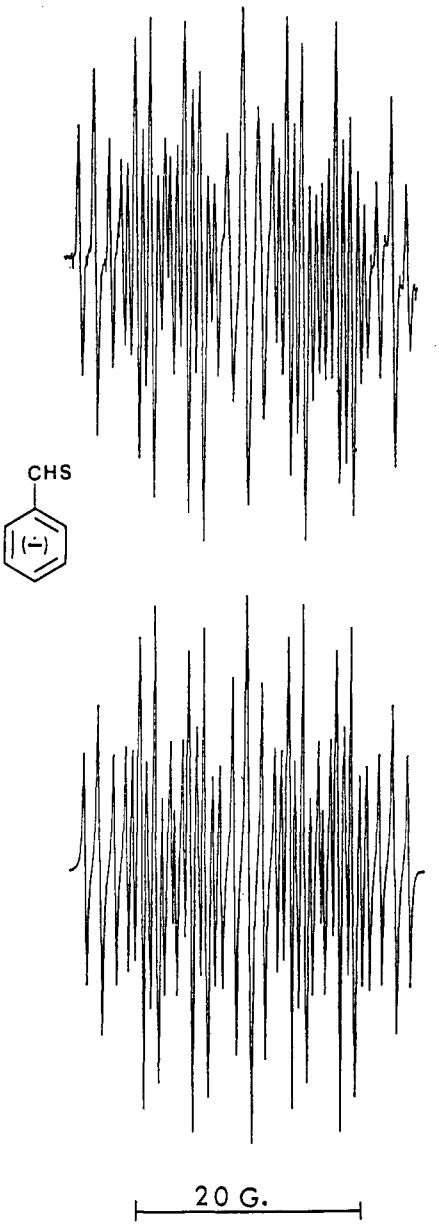

Figure 1. Experimental ESR spectrum (upper trace) of $PhCH{=}S^{\bullet-}$ (**2**) obtained by photolysis of $PhCH_2SH$ in EtOK/EtOH at room temperature. The computer simulation (lower trace) has been obtained with the a_H values listed in Table I and a line width of 0.2 G. To match the experimental intensities, the a_H splittings of H-3 and H-5 must differ by about 0.15 G.

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