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A Simple Method for *in situ* Generation of Thiols from Thioacetates

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Abstract: Thioacetates were converted to thiols by treatment with pyrrolidine in a variety of solvents. Second order rate constants were measured for the reaction in acetonitrile, DMF, methylene chloride, and THF. Thiols generated in this manner have been alkylated *in situ* with alkyl halides and α,β-unsaturated carbonyl compounds, providing a convenient way to produce various sulfides.

During the course of our work we wanted to convert thioacetate **1** to the corresponding thiol and subsequently alkylate with a carbapenem enol triflate **2**[1] to give sulfide **3.** Conditions for cleaving thioacetates modeled after literature conditions[2] ($NaHCO_3/H_2O/CH_3CN$ or NaOMe/MeOH) were either too slow or led to high amounts of disulfide. This led us to investigate the possibility of forming the thiol *in situ* and using it without isolation in an aprotic medium. We found that the treatment of **1** with one equivalent of pyrrolidine in acetonitrile (1 M, room temperature, 4 hours, argon atmosphere) conveniently produced thiol, which was then converted to **3**.

In general, we found that thioacetates were converted to thiols by treatment with pyrrolidine in a variety of solvents. Second order rate constants were measured by gas chromatographic analysis for the reaction in several solvents. The following order for the rate of cleavage of benzyl thioacetate in these solvents was observed: N,N-dimethylformamide (DMF) > acetonitrile > tetrahydrofuran (THF) > methylene chloride. However, the rates did not differ greatly in these solvents. It was found to be 1.7 times faster in DMF than in methylene chloride. Cleavage to thiol was approximately 1.5 times faster in methanol than in DMF, but it was not second order. A secondary alkyl thioacetate, cyclohexyl thioacetate, showed little difference in the rate of cleavage (1.1 times slower). A tertiary example, tert-butyl thioacetate, was converted to the corresponding thiol in DMF at rate that was 16.5 times slower than benzyl thioacetate.

Several nucleophiles other than pyrrolidine were investigated but were found to be less effective. Benzyl thioacetate was cleaved 13.9 times slower by piperidine and 7.7 times slower by propylamine than by pyrrolidine in DMF. Imidazole and 1,1-dimethylhydrazine were not effective and only provided traces of thiol. The presence of 0.27 equivalents of 4-dimethylaminopyridine (DMAP) along with pyrrolidine had no significant effect on the cleavage rate.

Thiols generated from alkyl thioacetates and pyrrolidine have been alkylated *in situ* with alkyl halides and α,β-unsaturated carbonyl compounds (Table). This method provided a convenient way to produce various sulfides from thioacetates in aprotic solvents without the need to isolate or purify the intermediate thiols while generating only a nonreactive by-product. It also provides a method complementary to other recently described procedures for the generation of thiols and sulfides from alkyl halides.[3]

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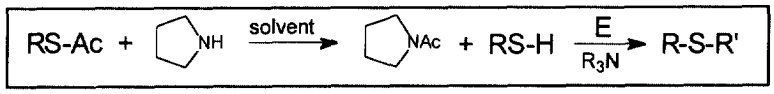
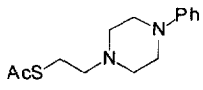
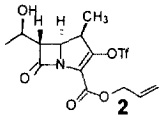
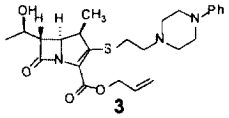
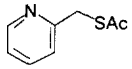
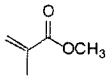
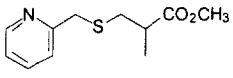
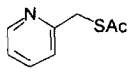
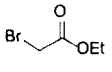
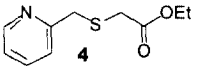
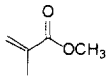
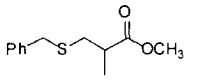
Table Preparation of sulfides from thioacetates.



RS-Ac	solvent	E	R-S-R'	% Yield (GC)
 1	CH_3CN	 2	 3	35 [4 steps]
	CH_3CN			67
	CH_3CN		 4	72
$PhCH_2SAc$	DMF	$PhCH_2Br$	$PhCH_2SCH_2Ph$	(87)
$PhCH_2SAc$	CH_3CN			(93)

Sample Procedure: Ethyl (2-picolylsulfenyl)acetate **4**

A 10 mL 2-neck flask containing 0.222 g (1.33 mmol) of 2-picolyl thioacetate was fitted with a septum, a gas inlet, and a magnetic stir bar and flushed with argon. The thioacetate was dissolved in 1.0 mL of anhydrous CH_3CN, and 0.111 mL (0.0946 g, 1.33 mmol) of pyrrolidine was added *via* syringe. After stirring at room temperature for 70 min 0.195 mL (0.142 g, 1.40 mmol) of triethylamine and 0.150 mL (0.226 g, 1.35 mmol) of ethyl bromoacetate were added, and the solution was stirred an additional 3 h at ambient temperature under argon before diluting with 10 mL of 1:1 ether : petroleum ether. This solution was extracted with 10 mL of water then 10 mL of brine, and the solution was dried over Na_2SO_4. After concentration 0.201 g (0.95 mmol, 72%) of ethyl (2-picolylsulfenyl)acetate **4** was obtained as a colorless liquid: TLC (SiO_2, Et_2O) R_f 0.39; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.1 Hz, 3H), 3.17 (s, 2H), 3.91 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 7.12 (dd, J = 7.6/4.8 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.60 (td, J = 7.6, 1.8 Hz, 1H), 8.52 (dm, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.1, 32.8, 38.1, 61.2, 122.0, 123.2, 136.6, 149.5, 157.6, 170.1.

References

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2. Zervas, L.; Photaki, I.; Ghelis, N. *J. Amer. Chem. Soc* **1963**, *85*, 1337.
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