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Mild, Selective Deprotection of Thioacetates using Sodium Thiomethoxide

Owen B. Wallace[a] and Dane M. Springer[b]

[a]Combinatorial Drug Discovery and [b]Central Chemistry,
Bristol-Myers Squibb Pharmaceutical Research Institute,
5 Research Parkway, Wallingford, CT 06492

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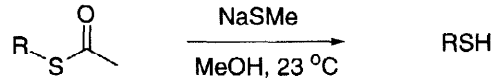
Abstract: A mild method for the deprotection of thioacetates is described. The reaction can be conveniently carried out at room temperature, and is compatible with a wide range of functionality. The procedure was shown to chemoselectively remove a thioacetate in the presence of an acetate.

The acetate has proven to be a versatile protecting group for the thiol functionality.[1] Although several methods for the deprotection of thioacetates have been reported,[2] they often involve harsh reaction conditions, expensive reagents, or are accompanied by significant disulfide formation.[3] While investigating the deprotection of polystyrene resin-bound thioacetates where use of ammonia proved problematic, we successfully explored the use of sodium thiomethoxide to effect this transformation. Herein, we report the scope of this method for the deprotection of thioacetates in solution.

Treatment of a methanolic solution of thioacetate at room temperature with sodium thiomethoxide cleanly affords the desired thiol.[4] The reaction is normally complete within minutes.



The procedure is remarkably mild and is compatible with a wide variety of functional groups. The deprotection is equally effective (Table 1) with primary thioacetates (entry 2), secondary (entry 8), tertiary (entry 6) and phenyl thioacetates (entry 7). More complex substrates also proceed in high yield. For example, deprotection occurs cleanly in the presence of an enone and lactone functionality (entry 1), carboxylic acid (entry 4),[5] hydroxyl (entry 6) and ester (entry 10). In order to examine the effect on a chiral centre, (-)-*N*,*S*-diacetyl-L-cysteine methyl ester (entry 10) was treated with NaSMe at 0 °C for 15 minutes, and the mixture subsequently quenched with Ac_2O; optically pure starting material was recovered. No elimination product was observed even with a sensitive succinimide substrate (entry 3). The mild conditions and good selectivity are further demonstrated in entry 5, where a thioacetate was selectively deprotected in the presence of a primary and secondary acetate.[6] The procedure is particularly useful for deprotecting volatile or water soluble thiols, which are conveniently isolated by concentrating to afford the sodium salt. The protocol is superior to simple basic hydrolysis or ammonia treatment in that the thiomethoxide can act as a sacrificial reductant, thus preventing oxidation of the desired thiol substrate.

The following procedure is representative: To a stirred solution of thioacetate (1 mmol) in methanol (10 mL) under nitrogen at 23 °C is added sodium thiomethoxide (1 equiv. 1M solution in MeOH). The reaction mixture is stirred at 23 °C for 30 minutes. The solution is then added to aqueous HCl

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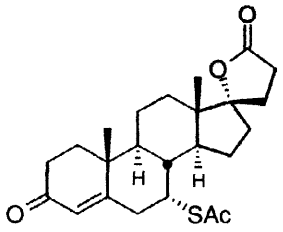
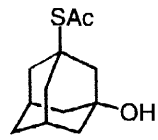
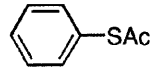
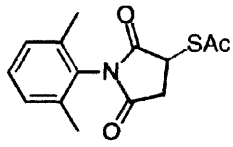
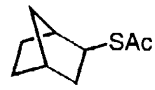
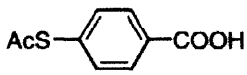
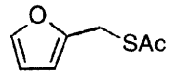
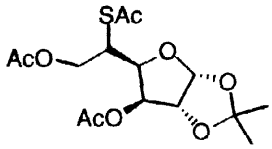
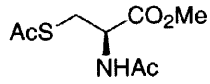
Table 1

Entry	Substrate	Yield	Entry	Substrate	Yield
1		95 %	6		96 %
2		91 %	7[b]		81 %
3[a]		97 %	8[b]		91 %
4		94 %	9[b]		92 %
5[a]		82 %	10[c]		> 95%

a) Reactions were carried out at -10°C. b) Isolated as the sodium salt. c) Due to instability of the product, yield obtained by quenching the reaction with 5 eq. $BrCH_2CO_2t$-Bu (95% yield of diester obtained).

20 mL/0.1M). The aqueous solution is extracted with CH_2Cl_2. The combined organic layers are washed with brine, dried over $MgSO_4$, filtered and concentrated. Products isolated as their sodium salts are obtained by concentrating the crude reaction mixture and triturating the resulting solid with ether to afford material which is generally analytically pure.

Acknowledgments

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References and Notes:

1 Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P.G.M. Eds. John Wiley & Sons, Inc.: New York, 1991.

2 See, for example: a) Chapman, J.H.; Owen, L.N. *J. Chem. Soc.* **1950**, 579. b) Baddiley, J.; Jamieson, G.A. *J. Chem. Soc.* **1955**, 1085. c) Bobbio, P.A. *J. Org. Chem.* **1961**, *26*, 3023. d) Endo, T.; Oda, K., Mukaiyama, T. *Chem. Lett.* **1974**, 443. e) Bianchi, D.; Cesti, P. *J. Org. Chem.* **1990**, *55*, 5657. f) Choi, J.; Yoon, N.M. *Synth. Commun.* **1995**, *25*, 2655.

3 Itokawa, H.; Kondo, K.; Hitotsuyanagi, Y.; Takeya, K. *Heterocycles* **1993**, *36*, 1837.

4 All compounds were characterised by NMR spectroscopy and MS or combustion analysis.

5 Treatment of this substrate with ammonia resulted in significant disulfide formation.

6 A similar reaction has been recently carried out using cysteamine as an acetyl transfer agent. Defaye, J.; Guillot, J.-M. *Carbohydr. Res.* **1994**, *253*, 185.