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A Novel Thiol Protecting Group: A 2-Thioquinoline Sulfide as a Masked Sulfhydryl Moiety

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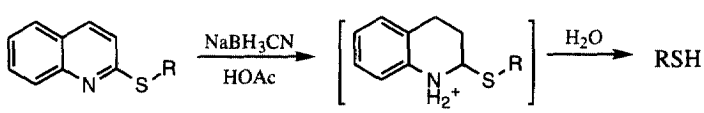
Abstract: 2-Thioquinoline sulfide was developed as a masked sulfhydryl entity. It is introduced through facile S_N2 displacement reactions and is stable to a variety of reaction conditions including acids, bases and nucleophiles. It is readily unmasked using the mild treatment of sodium cyanoborohydride in acetic acid.

Keywords: protecting group, thiol, quinoline and nucleoside.

The protection of a thiol is an important, yet sometimes troublesome, practice in organic synthesis. The commonly used thiol protecting groups include thioethers (benzyls and t-butyl), thioesters and disulfides.[1] However, all of these have limited scope of applications due to either unsatisfactory stability profiles or the harsh conditions that are required to deprotect. In the course of our study of 3'-thioformacetal linked oligonucleotides as antisense agents,[2] the need for a more general sulfhydryl protecting strategy emerged. We now describe our development of 2-thioquinoline sulfide as a masked sulfhydryl entity and its scope of synthetic applications.

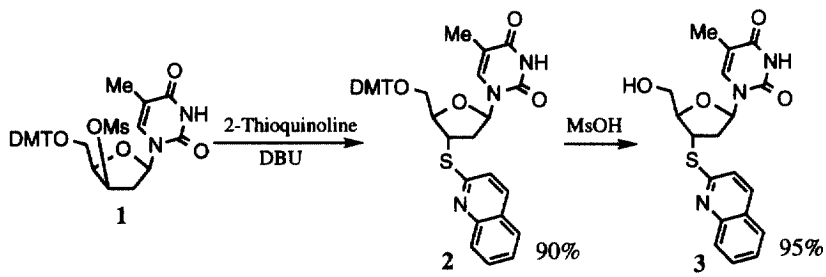
2-Quinolinethiol is commercially available and sulfides can be synthesized by simple S_N2 displacement reactions. Quinoline can be reduced under mild acidic condition such as acetic acid by $NaBH_3CN$.[3] We envisioned that reduction of a 2-thioquinoline sulfide would give a thioaminal intermediate which could be readily hydrolyzed to release the desired SH functionality (Scheme 1). 2-Thioquinoline sulfides should be stable to nucleophiles, something that the standard thiol protecting groups such as thioesters and disulfides are not.



Scheme 1

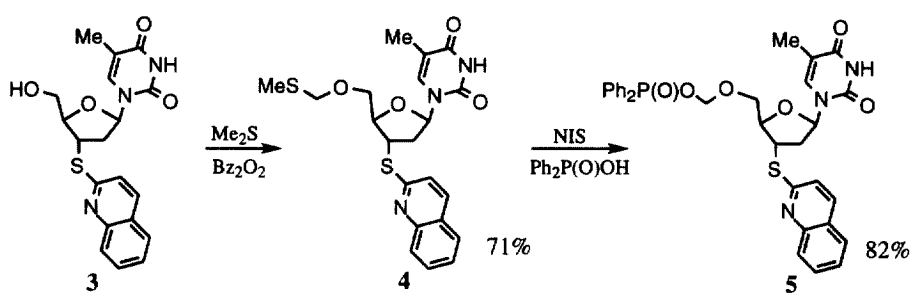
PII: S0040-4039(98)02694-X

We applied this strategy to the synthesis of the 3'-thioformacetal internucleotidic linkage. 2-Quinolinethiol was readily reacted with the thymidine analog **1** at 80 °C in DMF to give **2** in 90% yield (Scheme 2). Detritylation of **2** with methanesulfonic acid in $MeOH/CH_2Cl_2$ afforded **3** in 95% yield. To examine the stability profile of the 2-thioquinoline compounds, we subjected **3** to a variety of conditions including *concentrated NH_4OH at 60° C and the room temperature conditions of 1 N NaOH, 2N HCl, and saturated methanolic NH_3*, all for 24 h. No discernible decomposition was observed under any of the conditions tested.



Scheme 2

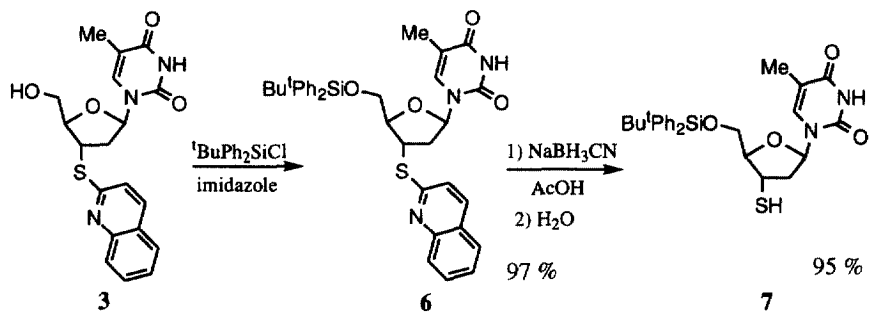
Compound **3** was further treated with Bz_2O_2/Me_2S to give methylthiomethyl ether **4** in 71% yield (Scheme 3). Compound **4** was then reacted with NIS and diphenyphosphinic acid to give **5** in 82% yield.[5] During this process, 2-thioquinoline moiety stayed completely intact. Its stability towards these mild oxidizing agents was noteworthy and was likely due to the electron deficient nature of the quinoline sulfide.



Scheme 3

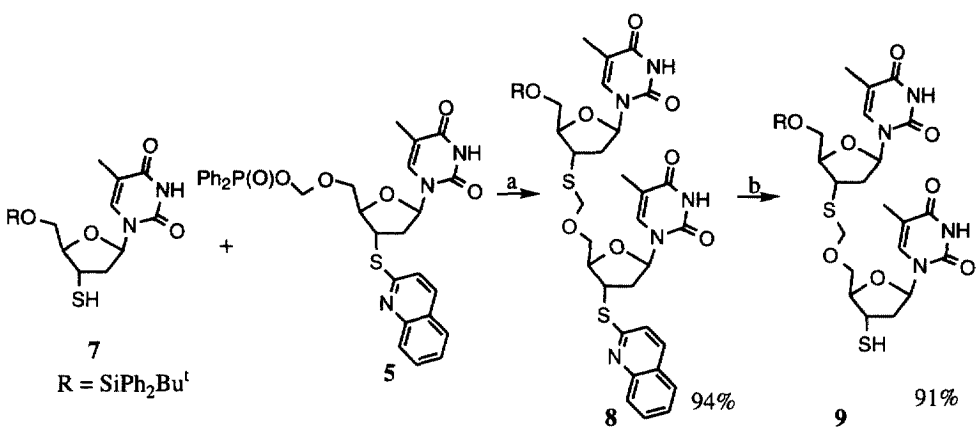
Deprotection was tested by first silylating **3** with t-butyldiphenylchlorosilane and imidazole in DMF to give **6** in 97% yield (Scheme 4). Unmasking of the thiol in **6** was performed with several equivalents of $NaBH_3CN$ in acetic acid followed by hydrolysis with H_2O.[6] After extractive workup, only the thiol form was isolated and no disulfide formation was observed.[7] $NaBH_3CN$ alone in organic solvent such as MeOH and CH_2Cl_2 could not effect the desired conversion, nor does $NaBH_3CN$ in the presence of two equivalent

of acetic acid in these solvents. This deprotecting process is fast and efficient and **7** was obtained in 95% yield.



Scheme 4

We further tested this strategy in a thiol coupling reaction. Compounds **7** and **5** was reacted under the reported conditions,[2b] and dimer **8** was obtained in 94% yield (Scheme 5). No undesired reaction was observed indicating that 2-thioquinolinyl group is stable to thiol in the presence of DBU. Further, dimer **8** can be unmasked to afford the free thiol compound **9** under the $NaBH_3CN$/AcOH conditions without affecting the thioformacetal moiety.



a) DBU, DMF/Formamide. b) $NaBH_3CN$/Acetic Acid, then H_2O

Scheme 5

In conclusion, the application of 2-thioquinolinyl group as a masked sulfhydryl is complementary to known sulfhydryl protection. It is stable to NaOH, HCl, concentrated ammonium hydroxide, methanolic ammonia, thiolate anion, mild oxidants and $NaBH_3CN$ under neutral conditions. In addition, it can be introduced to organic molecules through facile S_N2 displacement reactions. It can be readily unmasked under

mild conditions to give the sulfhydryl moiety. The broad stability profile and the ease of deprotection of the 2-thioquinolinyl strategy make it a useful option for thiol protections in organic synthesis.

References and Notes:

1. (a) Green, T. W.; Wuts, P. G. In *Protective Groups In Organic Synthesis* 2nd Edition; John Wiley & Sons: New York, NY, **1991**, p277. (b) Wolman, Y. In *Thiol Function* Patai, S. Ed.; John Wiley & Sons: London, **1974**, p669. (c) Bodansky, M. *Peptide Chemistry: A Practical Text Book* Springer-Verlag: Berlin, **1988**, p89.

2. (a) Jones, R. J., Lin, K.-Y., Milligan, J. F., Wadwani, S.; Matteucci, M. D. *J. Org. Chem.* **1993**, *58*, 2893. (b) Zhang, J.; Matteucci, M.D. *Tetrahedron Lett.*, **1995**, *36*, 8375. (c) Zhang, J., Shaw, J. T.; Matteucci, M.D. *Bioorganic &Medicinal Letters*, submitted.

3. (a) Gribble, G. W.; Heald, P. W. *Synthesis*, **1975**, 650. (b) Egucji, S., Matsushita, Y. and Takeuchi, H. *J. Org. Chem.* **1992**, *57*, 6925.

4. 2-Quinolinethiol is commercially available from Aldrich, and Pfaltz and Bauer.

5. Medina, J. C., Salomon, M.; Kyler, K. S. *Tetrahedron Lett.* **1988**, *29*, 3773.

6. Typical procedure for unmasking of 2-thioquinoline compounds: To a stirred solution of the 2-thioquinoline sulfide **6** (3.6 g, 6.4 mmol) in glacial acetic acid(120 mL), was added in several portions of $NaB(CN)H_3$ (2.0 g, 32 mmol) in a period of 2 h. The reaction mixture was further stirred for one additional hour. H_2O (20 mL) was added to the reaction mixture and stirring was continued for 30 min. Concentration of the reaction mixture and extraction with CH_2Cl_2 afforded the desired sulfhydryl functionality, which can be purified by chromatography with 2% MeOH in CH_2Cl_2 to give 3.1 g of thiol **7** in 95% yield.

7. It was sometimes difficult to avoid the formation of a small amount of disulfide during deprotection of thioesters with hydroxides or ammonia because the basic condition accelerated disulfide formation.