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PII: S0040-4039(18)31324-8
DOI: https://doi.org/10.1016/j.tetlet.2018.11.008
Reference: TETL 50393

To appear in: *Tetrahedron Letters*

Received Date: 7 September 2018
Revised Date: 31 October 2018
Accepted Date: 4 November 2018

Please cite this article as: Wang, T-L., Liu, X-J., Zhang, X., Cao, B-Q., Quan, Z-J., Wang, X-C., UV light enabled methylation of quinoline-2-thione using dimethyl sulfoxide to give quinoline methyl sulfide, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.11.008

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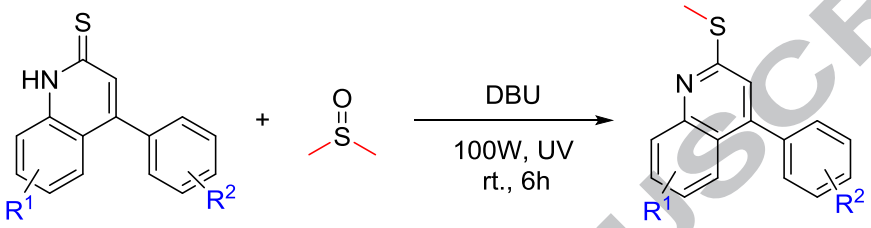

R^1 = Cl, alkyl
R^2 = Cl, F, alkyl

16 examples
up to 92% yield

Tetrahedron Letters
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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
UV light
Dimethyl Sulfoxide
Methyl Sulfide
Quinoline-2-thione

ABSTRACT

An UV-light-induced *S*-methylation of quinoline-2-thione was completed by using dimethyl sulfoxide as methyl reagent. A series of quinoline methyl sulfides were prepared in moderate to good yields under environmentally friendly and mild conditions.

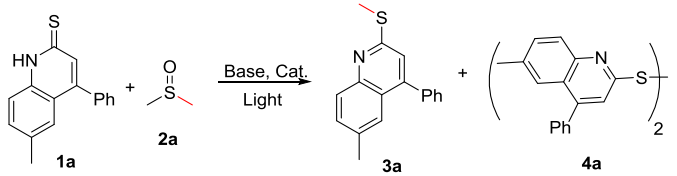
Introduction

Dimethyl sulfoxide (DMSO) which chemical formula is $(CH_3)_2SO$ is a common organic sulfur compound. In many organic synthesis, DMSO is used as a cheap, low-toxic and well-dissolved common aprotic polar solvent[1] and served in many well-known multi-agent reagent name reactions, such as Swern oxidation,[2a] Pfitzner-Moffatt oxidation,[2b] and Corey-Chaykovsky reaction.[2c] In addition, deuterated DMSO can also be used as a solvent for analytical studies, especially in ^{1}H NMR and ^{13}C NMR, and it is often used in the study of reaction kinetics. Except its important value in organic synthesis, DMSO is also widely used in the pharmaceutical industry, such as the research and treatment of rheumatic diseases.[3] Currently, it is approved as an active pharmaceutical ingredient (API).[4] Experiments and clinical studies have been shown that DMSO has the same effect with some non-steroidal anti-inflammatory drugs to prevent inflammation such as drugs (NSAIDs).[5] Therefore, DMSO is favored by numerous chemical researchers.

The quinoline backbone is a common structure in many bioactive natural products, drugs and materials.[6] Methyl sulfide compounds also play an important roles in many areas of biological and life science materials, especially in the pharmaceutical industry. These scaffolds are found in natural 、non-natural products and exhibited good activity in against cancer, AIDS, Alzheimer's disease, inflammation and asthma. [7] Therefore, methylation is an important reaction in organic synthesis and biological processes. Common methods for synthesizing methyl sulfides generally include i) reduction of sulfoxides.[8] ii) using methyl iodide,[9] dimethyl sulfate,[10] and dimethyl carbonate[11] as methylation reagents of thiophenols/thiols.[12] iii) directed or heteroatom-assisted activation of aromatic C-H bonds and SEAr reaction with dimethyl disulfide.[13] In recent years, DMSO has been widely used as a methyl source in organic synthesis due to its various advantages.[14] Csp^2-H methylation,[15] N-H methylation,[16] and COO-H methylation[17] have been reported. However, thiomethylation by DMSO as a source of CH_3 is rarely reported. Herein, we reported a method for the efficient synthesis of quinoline methyl sulfide compounds based on our previous work.[18]

We began our investigation by examining the methylation of 6-methyl-4-phenylquinoline-2(1H)-thione (**1a**) with DMSO (**2a**) (Table 1). As expected, there was no methylation product **3a** formed without photocatalyst and light, but the disulfide **4a** was obtained in 46% isolated yield (Table 1, entries 1 and 2). Next, we tested the light sources and photocatalysts. Irradiated the reaction with visible lights (such as green and blue lights) in the presence of photocatalysts such as Eosin Y and $Ru(bpy)_3Cl_2$, we fortunately obtained the expected target product **3a** in about 20% yield along with forming the **4a** as the major product (Table 1, entries 3-6). To improve the selectivity and yield of **3a**, the reaction was performed with 300 W UV without photocatalyst provided a higher yield of **3a** (43% vs 20%) (Table 1, entry 7 vs entries 3-6). However, a mixture of 23% yield of **4a** and other by-products was also obtained, which may be due to the UV intensity adversely affect the formation of free radicals. Then, we observed a significant increase in yield of **3a** with 100W UV (Table 1, entries 8 and 9). Finally, we got the optimal conditions in the presence of 20 mol% of DBU with 100W UV to provide the methylation product in a 92% yield (Table 1, entry 10).

Table 1. Optimization of Reaction Conditions[a]



Entry	Light	Cat.	Base (20%)	Yield/%[b] 3a	Yield/%[b] 4a
1	---	---	---	---	46
2	---	---	DBU	---	53
3	Green (>495 nm)	---	DBU	20	72
4	Green	Eosin Y	DBU	26	65
5	Blue (>476 nm)	Eosin Y	DBU	18	74
6	Blue	$Ru(bpy)_3Cl_2$	DBU	22	70
7	UV (300 W) (365 nm)	---	---	43	23
8	UV (100 W) (365 nm)	---	---	82	trace
9[c]	UV (100 W)	---	---	86	trace
10[c]	UV (100 W)	---	DBU	92	trace

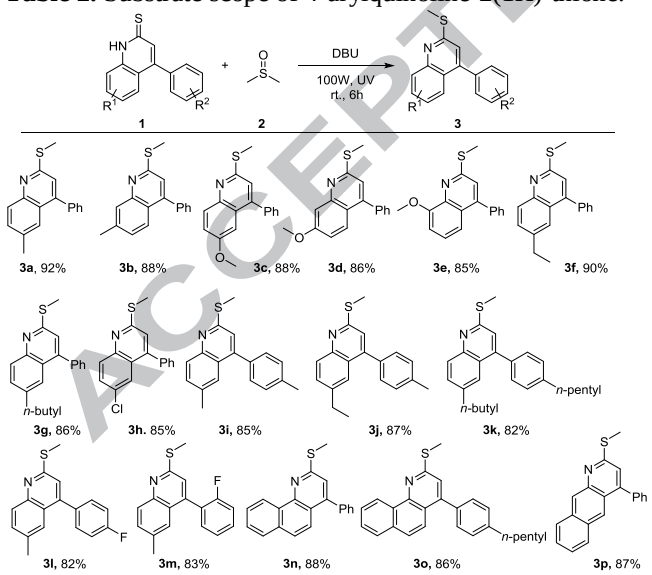
[a] Reaction conditions: **1a** (0.2 mmol), **2a** DMSO (2 mL), DBU (1,8-diazabicycloundec-7-ene) (20 mol%), rt, 6 hours, 100 W UV.

[b] Isolated yield.

[c] 4 mL DMSO was used.

With the optimal conditions in hand, then we examined the substrate scope (Table 2). As shown in Table 2, a wide range of quinoline-2(1H)-thiones which have different substituents could give the corresponding methyl sulfide in moderate to good yields. Neither the electron withdrawing group nor the electron donating group affects the yield. The halide (-F, -Cl) substituent was well tolerated under these conditions and therefore provides an opportunity for further conversion. In addition, fused aromatic hydrocarbons (**3n~3p**) were also suitable for this method.

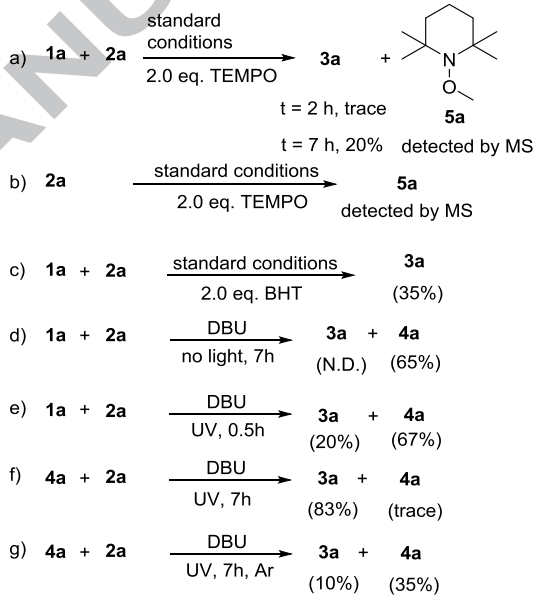
Table 2. Substrate scope of 4-arylquinoline-2(1H)-thione.[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), **2a** DMSO (4 mL), DBU (20 mol%), rt, 6 hours, 100 W UV.

[b] Isolated yield.

To understand the methylation reaction mechanism, we did a series of radical trapping experiments and control experiments. Under standard conditions (Scheme 1a), 2 equivalents 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction mixture and a trace amount of **3a** could be detected after 2 hours. After 7 hours, 20% of product **3a** was collected and 1-methoxy-2,2,6,6-tetramethylpiperidine **5a** was detected by MS analysis. Also, under the standard conditions, **1a** was not added, and after the end of the reaction, **5a** was detected by MS analysis (Scheme 1b). Another radical scavenger, butylated hydroxytoluene (BHT) was also tested and it was collected 35% of **3a** (Scheme 1c). These results indicate that a free radical pathway was involved and in this reaction methyl radicals may be produced as free radical intermediates. **4a** was obtained as the main product without light and **3a** was not detected (Scheme 1d). At the same time, it was found that **1a** was rapidly consumed and the corresponding 1,2-bis(6-methyl-4-phenylquinolin-2-yl)disulfide **4a** was produced in the first 0.5 hours in a yield of 67%. The yield was gradually reduced during the reaction undergoing (Scheme 1e). When **4a** was treated under standard conditions **3a** was obtained in 83% yield (Scheme 1f). Hence it was speculated that UV might be crucial for the transformation of DMSO to methyl radicals. Finally, we found that the reaction of **1a** and **2a** under Argon atmosphere produced **3a** and **4a** in a yield of 10% and 35%, respectively (Scheme 1g). This result indicated that the air (O_2) involved in this reaction and it is essential for the methylation process.

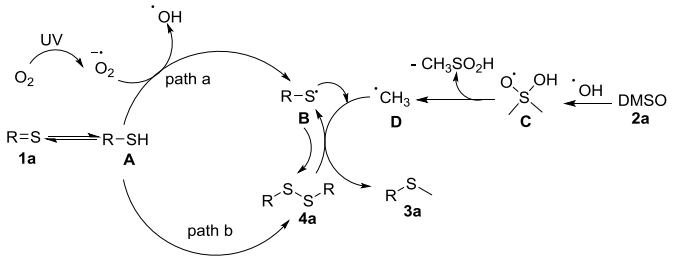


Scheme 1. Mechanistic Studies.

Based on the above experimental results and previous reports,[19] we proposed the possible mechanism of the reaction between **1a** and **2a** (Scheme 2). Initially, **1a** tautomerizes into a thio intermediate **A**.[20] O_2 (air) produces peroxyl radical $O_2^{\cdot-}$ under UV, which interact with intermediate **A** to form a hydroxyl radical and a sulfur radical **B** (path a). Intermediate **B** undergoes dimerization to produce disulfide **4a**. Alternatively, **1a** is directly oxidized by DMSO or air to form **4a** (path b). Hydroxyl radical is added to DMSO to form intermediate **C**, and then **C** undergoes *ß*-cleavage to give methyl radical **D** and CH_3SO_2H which was detected by GC-MS at m/z 81.0 (M+1). The methyl radical **D** is directly coupled to the sulfur radical **B** or radically substituted with the intermediate **4a** to give **3a**.

In summary, we have developed a heterocycle *S*-methylation strategy enabled under UV light using DMSO as a carbon source. The reaction can afford desired products in moderate to good yields under mild and environmentally friendly conditions. Therefore, this strategy is likely to be a viable and low-cost alternative to the traditional method of preparing methyl sulfide compounds. Further investigation to determine the mechanism of

this reaction and to expand its scope is underway in our laboratory.



Scheme 2. Proposed mechanism.

Acknowledgments

We are thankful for the financial support from the National Nature Science Foundation of China (No. 21562036) and the Scientific and Technological Innovation Engineering program of Northwest Normal University (NWNU-LKQN-15-1).

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Highlights

1. Methylation of quinoline-2-thione under mild and environmentally friendly conditions.

2. DMSO as readily available source of methyl group

3. Using UV light without metal- and dye-photocatalyst.