Isothiazole Ring Formation with Substituted 2-Alkylthio-3-acyl-4-quinolinone Using *O*-(Mesitylenesulfonyl)hydroxylamine (MSH)

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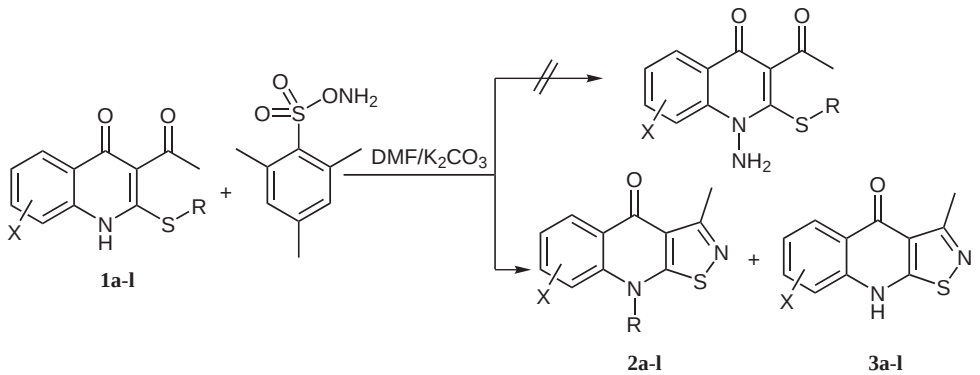
Abstract: Isothiazole ring skeleton was formed by the treatment of substituted 2-alkylthio-3-acyl-4-quinolinone with *O*-(mesitylenesulfonyl)hydroxylamine(MSH). A mixture of alkyl transferred 3-methyl-9-alkyl-4,9-dihydroisothiazolo[5,4-*b*]quinolin-4-one as a major product and dealkylated 3-methyl-4,9-dihydroisothiazolo[5,4-*b*]quinolin-4-one as a minor product was obtained from unsubstituted 2-alkylthio-3-acyl-4-quinolinone in the presence of K_2CO_3. When 2 equivalents of MSH were used in the absence of K_2CO_3 only dealkylated product was obtained in quantitative yield.

Key words: imine, electrophilic addition, cyclizations, isothiazole, *O*-(mesitylenesulfonyl)hydroxyl amine

Isothiazole moiety either fused or isolated form has been frequently found to play an important role in various biological activities such as an anti-inflammatory,[1] antifungal,[2] antibiotics,[3] antiviral,[4] cholesterol lowering agent,[5] microbicide,[6] and agrochemical.[7] Numerous methods of preparation of fused isothiazoles such as benzoisothiazoles,[8] quinolinoisothiazoles,[9] and other heterocylic isothiazoles[10] or of isolated isothiazoles[11] have been very well documented. Among others, cyclizations of aliphatic substrates or aromatic substrates containing sulfenamide, thiocyanato, alkylthio or thiol group adjacent (ortho position) to aldehydes, or esters group are common in the presence of a condensing agent such as hydroxylamine, hydroxylamine-*O*-sulfonic acid as a nitrogen source for isothiazole.[10–12] Mostly, it is necessary for sulfur atom to bear good leaving group like NH_2, CN, or Cl to accommodate nucleophilic attack by nitrogen atom condensed with aldehyde or ester. An alkylthio or thiol group is first converted into sulfenyl chloride with sodium hypochlorite, thionyl chloride or sulfuryl chloride as an acceptor for nitrogen.[8d,11,12b] To the best of our knowledge, the only published example of the addition of a sulfur atom to nitrogen as an alkylthio group was the cyclization of 2-ethylthio-3-*O*-acetylaldoxime quinoline to yield isothiazoloquinoline.[9c] Cleavage of the ethyl group from the ethylthio group was explained by the intramolecular transfer of the ethyl group to an acetate group in the oxime acetate dipolar complex, to ultimately producing ethyl acetate.

Here we report direct fused isothiazole ring formation by *O*-(mesitylenesulfonyl)hydroxylamine (MSH) which has never been employed as a condensing agent to yield an isothiazole ring. In the literature MSH has been known to deliver its amino moiety as an electrophile to a number of different atoms such as nitrogen,[13] sulfur,[14] or phenolic oxygen[15] and to undergo condensation with carbonyl group.[16]

In the beginning we attempted N-amination of 2-methylthio-3-acylquinolin-4-one (**1a**) with MSH as described in the literature[17] to prepare *N*-aminoquinolinone which, in turn, was needed for our ongoing program to prepare biologically active molecules for a new agrochemical purpose (Scheme 1). Instead of *N*-aminoquinolinone, we unexpectedly obtained a mixture of dihydroisothiazoloquinolinones **2** and **3** of which structures were identified unambiguously by X-ray crystallography as shown in Figure 1 and Figure 2.[18]



Scheme 1

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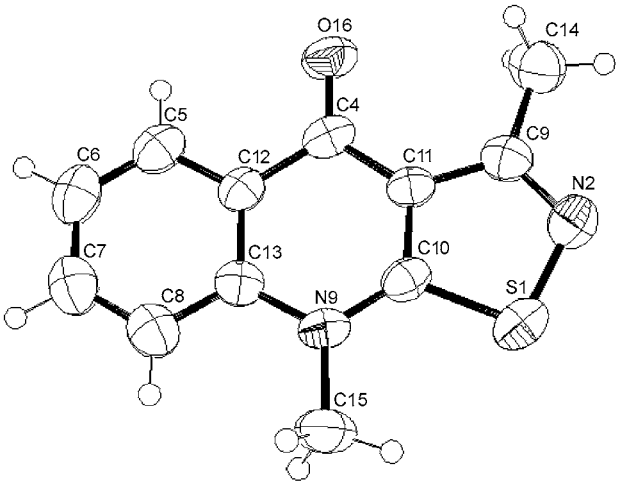


Figure 1 X-ray structure of **2a** at the 50% probability level

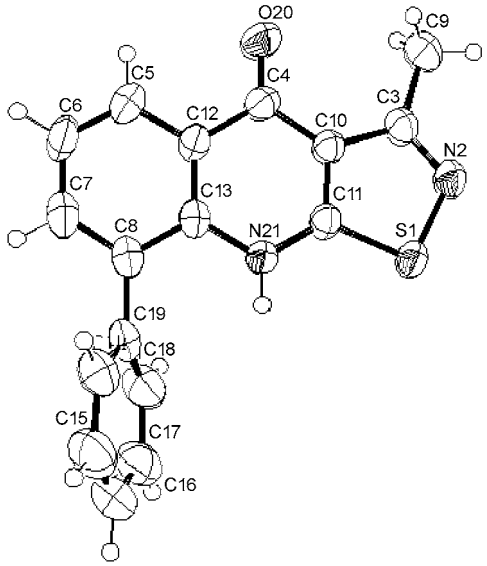


Figure 2 X-ray structure of **3f** at the 50% probability level

Results for various isothiazole formation are summarized in Table 1.[19]

It is obvious from entry **1a**–**d** that these substrates provide the same dealkylated isothiazole product **3** regardless of the character of R group.

Yield of the minor product **3** varies from 10% to 40% depending on the type of alkyl group. Yield of the phenyl group is the lowest. In the case of **1j**, evaporation of the solvent under vacuum at room temperature resulted in the decomposition of residue. The product was isolated at 0 °C to prevent decomposition. The only product isolated was the corresponding dealkylated isothiazole **3j** without any trace of N-methylated product. In addition MSOMe was always isolated in minute quantity (ca. 8%). Drastic changes in the product ratio of **1j** and **ik** can be explained by difference in σ_p where Br exhibits more electron withdrawing power so that the proton on nitrogen atom

Table 1 Product Yields of Dihydroisothiazoloquinolinones **2** and **3**[a]

Substrate (**1**)	X	R	Product yield (%)		Mp (°C)	
			2	**3**	**2**	**3**
1a	H	Me	55	30	199–200	342–344
1b	H	*n*-Pr	45	40	125–126	342–344
1c	H	Bn	57	22	181–182	342–344
1d	H	Ph	55	10	177–179	342–344
1e	8-Et	Me	20	40	211–212	262–263
1f	8-Ph	Me	60	10	189–190	284–285
1g	6-*t*-Bu	Me	22	42	183–185	291–293
1h	6-MeO	Me	63	11	208–209	330–331
1i	6-C1	Me	61	19	241–243	339–340
1j	6-C1	Me	0	70[b]	–	258–259
	8-CF_3					
1k	6-Br	Me	55	0[c]	145–147	–
	8-CF_3					

[a] Reaction condition: see ref.[19]
[b] Work-up was performed at 0 °C due to instability of the product during isolation.
[c] Significant amount (22%) of N-amination product was observed.

become more acidic. Efforts have been made to optimize reaction condition as can be seen in Table 2. Depending upon the amount of K_2CO_3, product yields changed dramatically.

Although more than 70% of the starting material was recovered, demethylated product **3a** was obtained as a single product in a high conversion rate when less than 1 equivalent of K_2CO_3 is was used. Even without it the reaction proceeded to give only product **3a**. To complete the reaction 2.5 equivalents of K_2CO_3 was required. Additional amount did not affect the yield and ratio of the product mixture. Surprisingly, when an excess amount of MSH (2 equiv) was employed in the absence of K_2CO_3 the reaction was completed within 5 minutes furnishing **3a** quantitatively as a single product (entry 5). However, the amount of MSOMe isolated was approximately the same as before in 8% yield. Addition of K_2CO_3 almost did not affect yield of **3a** except that minute amount of O-methylated product (2–3%) instead of MSOMe was obtained. Various substrates are subjected under these reaction conditions and the results are summarized in Table 3.

The reaction of quinolinones proceeded so rapidly that the substrate disappeared completely at room temperature and the product **3** was precipitated within 5 minutes. Approximately the same amount (ca. 8%) of MSOMe was obtained regardless of substituent of quinolinone. Assuming the only fate of methyl group is to form MSOMe, far less MSOMe was isolated than expected. In the case of entry 7, a mixture of **3** and N-aminated product was obtained in 52% and 32% yield respectively.

When cyano group instead of acyl group is substituted like entry 9, it was inert to the reaction condition.[8a,9a] We can isolate MSOH in an aqueous layer from hydrolysis of an ion pair or/and from the remaining MSH during the work up. This was verified by isolating MSOH after treatment of MSH in aqueous DMF (10 equiv H_2O).

Table 3 Product Yields of Dihydroisothiazoloquinolinones **3**[a]

1 **3**

Entry	Substrate **1** (X =)	Yield (%)[b] of **3**
1	H	99
2	6-OMe	98
3	8-Et	100
4	8-Ph	99
5	6-Cl	98
6	6-Cl, 8-CF_3	98
7	6-Br, 8-CF_3	52[c]
8	S-Bn[d]	100
9	8-MeO, 3-CN	0

[a] 2 Equiv of MSH was used in the absence of K_2CO_3.
[b] Isolated yield.
[c] Mp138–140 °C, significant amount (32%) of N-amination product was obtained.
[d] X = H, S-Bn instead of S-Me.

In order to clarify the fate of the methyl group ^{1}H NMR (500 MHz) was run at a concentration diluted by one fifth of the real reaction condition in DMF-d_7 in order to avoid precipitate of product.[20] According to the analysis of ^{1}H NMR, MeOH and MSOH peaks appeared early in the reaction at δ = 3.284 ppm (OMe) and δ = 6.824 ppm (aromatic) respectively. As the reaction proceeded, a new peak at δ = 3.706 ppm (OMe) gradually increased and

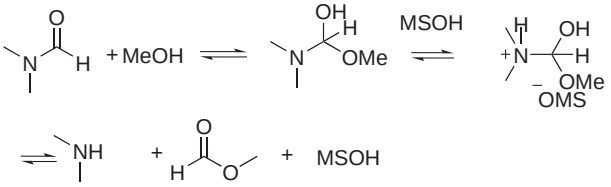
Table 2 Reaction of 2-Thiomethyl-3-acylquinolin-4-one (**1a**)[a]

Entry	MSH (equiv)	K_2CO_3 (equiv)	Reaction time	Yield (%)[b]			
				1a	**2a**	**3a**	MSOMe
1	1	0	4 h	70	0	24[c]	7
2	1	1	4 h	72	0	20	9
3	1.1	2.5	4 h	0	55	30	8
4	1.1	3.5	4 h	0	55	30	8
5	2	0	5 min	0	0	98	8
6	2	1	15 min	0	0	97	0[d]
7	2	2.5	15 min	0	0	98	0[d]

[a] Reaction was run in DMF at r.t.
[b] Isolated yield.
[c] Addition of 1 equiv and 10 equiv of H_2O did not change product yield.
[d] Small amount (2–3%) of 4-methoxy-3-methylisothiazoloquinoline was obtained.

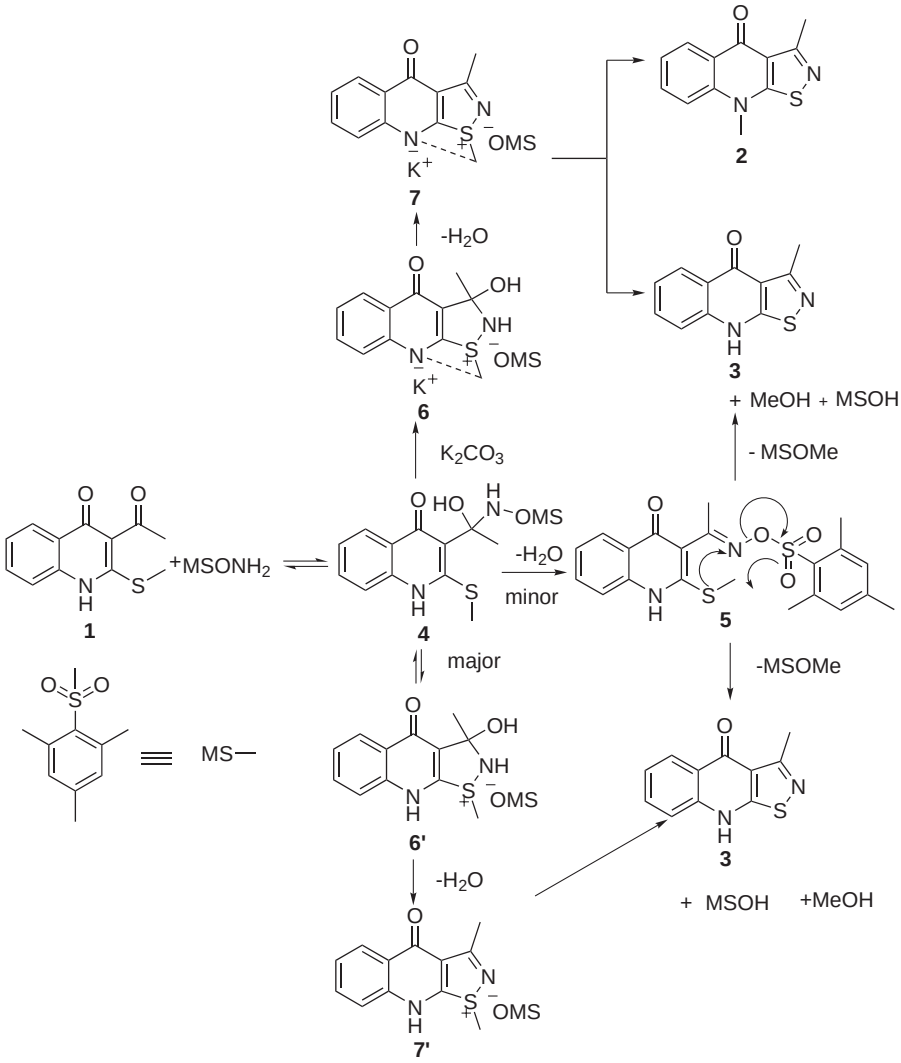
reached its maximum after 2 hours. By comparing its ^{1}H NMR in DMF-d_7 and GCMS[21] spectra to an authentic sample, it was characterized as methylformate. In addition, the presence of a small amount of MSOMe was confirmed by an authentic sample prepared separately by reacting MSCl with MeOH as solvent in the presence of Et_3N. Corresponding peaks of MSOMe (OMe: δ = 3.711 ppm, 2 H aromatic: δ = 7.011 ppm) appeared at the early stage of the reaction (within 5 min) in a small amount and remained during the whole reaction period. Possibility to transfer methyl group from MSOMe to **3a** has been excluded after control experiment treating **3a** with MSOMe in the presence of K_2CO_3. Reaction did not proceed at all. While all of the aromatic protons (δ = 7.116 ppm) of MSH disappeared, those of MSOH (δ = 6.824 ppm) protons kept increasing. Even after the substrate peaks disappear, further decrease of MSH peaks was observed.

Based upon a time dependant stack plot analysis of ^{1}H NMR, a plausible mechanism can be depicted as displayed in Scheme 2. It can be explained that the incipient ion pair **7′** undergoes hydrolysis by H_2O generated from cyclized adduct **6′** to produce MeOH and MSOH. Once MeOH is generated, it is trapped by the solvent to form dimethylformamide hemiacetal,[22] which was consequently split into dimethylamine and methylformate as indicated in Scheme 3.



Scheme 3

A control experiment verified in DMF reacting MSH with MeOH in the presence of catalytic amount of MSOH that disappearance of the MSH aromatic peak was followed by appearance of methylformate peak. Since MSH is known

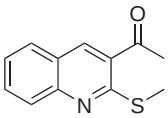
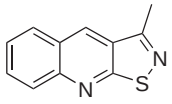
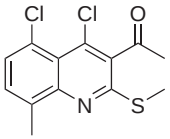
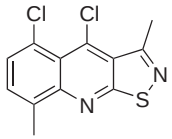
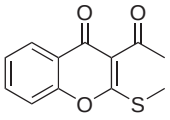
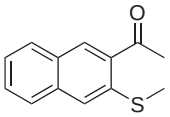
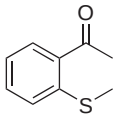


Scheme 2 Mechanism for the formation of dihydroisothiazoloquinolinone

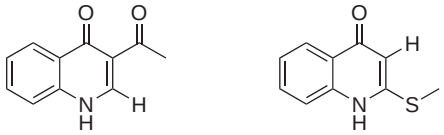
to decompose by itself to nitrogen, hydrazine and MSOH,[23] an excess amount of MSH is required to complete the reaction. Since MSOMe was produced in small quantities and stayed constant during the reaction a dual reaction pathway seemed to be operating. A major pathway is forming the ion pair **7′** from tetrahedral intermediate **4** and a minor pathway is the oxime **5** formation, which undergoes cyclization to provide MSOMe.[9c,d] Thus the methyl group of thiomethyl ended up as MeOH, methylformate, and MSOMe via the competitive reaction of forming ion pair **7′** and oxime **5**. Thus, once MSOH and/or H_2O are generated, the remaining MSH will be rapidly destroyed unless equilibrium is shifted to the far right. The equilibrium shift forms tetrahedral intermediate **4** so that one equivalent of MSH should be used up quickly to form product. In comparison with the equimolar reaction, the excess amount of MSH must have played a role shifting equilibrium to tetrahedral intermediate so that equivalent amount of MSH was used up quickly before it decomposed. Remaining MSH must have been decomposed either by itself or by reacting with other species as mentioned above. Depletion of H_2O peak (δ = 3.299 ppm), which was appeared at the beginning of the reaction was observed in ^1H NMR indicating that H_2O was used up in the course of reaction. When K_2CO_3 is present, potassium salt of **7′** can be assumed to be **7**. In addition, the same reaction as intemediate **7′** intramolecular methyl transfer to nitrogen anion in ion pair **7** can occur via four membered [1,3]thiazeto transition state, of which its existence can be supported by recent examples of the synthesis of [1,3]thiazeto[3,2*a*]quinoline-3-carboxylic acids.[24] The fact that the use of one equivalent of K_2CO_3 did not provide **2** means that it is not sufficient large enough to generate a nitrogen anion. The optimal amount of K_2CO_3 was 2.5 equivalent, which in turn, obtained at maximum yield of **2**.

In order to expand the scope, the reaction was attempted with a few different skeletons. Substrates were prepared according to the known procedures.[25] The results are summarized in Table 4. Quinoline (entry 1–2) also furnished the corresponding isothiazole in excellent yields which exhibited strong fluorescent under UV lamp. However, reaction did not take place with similar skeletone like chromone (entry 3) and naphthalene (entry 4). Even after 8 hours of prolonged stirring, starting material is recovered completely. According to MOPAC PM3 calculation for electrophilic superdelocalizability[26] of carbonyl carbon it looks similar for entry 1, 3 and 4. However, that of N, O and C in the aromatic region is quite different from each other. Although transition state calculation between MSH and the substrate adduct has not been performed, richer electron density might be developed at carbonyl carbon of the substrate due to larger value of superdelocalizability of N compared to O or C so as to attract MSH more favorably. In spite of being contradictory to the normal nucleophilic attack to carbonyl carbon, it might be due to amphiphilic nature of MSH nitrogen. Efforts to distinguish reactivity between nucleophilic oxime formation and electrophilic sulfilimine was made without success. A reaction of quinolinone **8** and **9** with MSH to isolate an imine adduct or sulfilimine did not proceed at all (Figure 3).[27] Thus it is difficult to determine which route is preferable at the moment.

Table 4 Product Yields of Isothiazoles with Various Substrates[a]

Entry	Substrate	Product	Yield (%)[b]
1			100[c]
2			88[c]
3		–	0[d]
4		–	0[d]
5		–	0[d]

[a] 2 Equiv of MSH was used in the absence of K_2CO_3.
[b] Isolated yield.
[c] Starting material was recovered after 86 h.
[d] Strong fluorescent.



8 **9**

Figure 3

In conclusion an isothiazole ring can be constructed easily with 2-alkylthio-3-acyl-4-quinolinones and with 2-alkylthio-3-acyl-quinolines under simple and mild conditions employing *O*-(mesitylenesulfonyl)hydroxylamine (MSH) as a condensing agent.

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(18) X-ray crystal structure analysis of **2a** and **3f**: Atomic coordinates, bond lengths [Å] and angles [deg], anisotropic displacement parameters, hydrogen coordinates, torsion angles [deg] have been deposited at Cambridge Crystallographic Data Centre 12, Union Road. Cambridge. CB2 1EZ, UK. Under deposition number CCDC 192773 for **2a**,CCDC 192772 for **3f** (Fax: +44(1223)336033, E-mail:deposit@ccdc.cam.ac.uk).

(19) **Representative Procedure**: To a stirred solution of (**1a**) (300 mg, 1.28 mmol) in DMF (3 mL) was added K_2CO_3 (442 mg, 3.2 mmol). After Stirring for 30 min at r.t., MSH (304 mg, 1.41 mmol) was added in small portion during the period of 1 h. The mixture was stirred at r.t. for 4 h. The solvent was distilled off, and the residue was partitioned between EtOAc (500 mL) and H_2O (80 mL). The organic layer was separated, washed with brine (50 mL), and dried with anhyd $MgSO_4$. After filtering $MgSO_4$, the solvent was evaporated under vacuum to give a mixture of crude products (267 mg) which was separated by column chromatography (hexanes:EtOAc = 3:1) to afford 3,9-dimethyl-9*H*-isothiazolo[5,4-*b*]quinolin-4-one (**2a**) (162 mg, 55%), 3-methyl-9*H*-isothiazolo[5,4-*b*]quinolin-4-one (**3a**) (83mg, 30%) and 2,4,6-trimethyl-benzenesufonic acid methyl ester (22 mg, 8%). (**2a**) Yield: 55%, Yellow solid, R_f = 0.41 (CH_2Cl_2:MeOH = 30:1), mp 199–200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56–8.51 (m, 1 H), 7.79–7.70 (m, 1 H), 7.46–7.37 (m, 2 H), 3.84 (s, 3 H), 2.89 (s, 3 H).^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.16, 170.24, 168.23, 140.61, 133.17, 127.51, 125.60, 123.29, 118.99, 113.69, 38.46, 21.09. MS: *m/z* = 230 (M^+), 215, 197, 184, 169. HRMS (EI): calcd for $C_{12}H_{10}N_2O_1S_1$: 230.0517. Found: 230.0520. Anal. Calcd for $C_{12}H_{10}N_2O_1S_1$: C, 62.59; H, 4.38; N, 12.16; S, 13.92. Found: C, 62.61; H, 4.41; N, 12.55; S, 13.83. (**3a**) Yield: 30%, Yellow solid, R_f = 0.08 (hexanes:EtOAC = 3:1), mp 342–344 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 12.75 (s, 1 H), 8.25–8.22 (m, 1 H), 7.78–7.71 (m, 1 H), 7.53–7.49 (m, 1 H), 7.40–7.33 (m, 1 H), 2.72 (s, 3 H).^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.75, 165.97, 165.24, 140.07, 133.20, 125.93, 123.55, 122.93, 118.64, 117.60, 20.35. MS: *m/z* = 216 (M^+), 199, 183, 170, 161. HRMS (EI): calcd for $C_{11}H_8N_2O_1S_1$: 216.0360. Found: 216.0357. **2,4,6-Trimethyl-benzenesufonic Acid Methyl Ester**: Yield: 8%, Yellow oil, R_f = 0.76 (hexanes:EtOAc = 3:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.99 (s, 2 H), 3.70 (s, 3 H), 2.63 (s, 6 H), 2.32 (s, 3 H). MS: *m/z* = 214 (M^+), 196, 182, 174, 165, 149.

(20) ^{1}H NMR was run in Bruker AMX 500MHz in DMF-d_7. A mixture of MSH (22 mg) and **1a** (12 mg**)** in 1mL of DMF-d_7 was used and the spectrum was run at an interval of 5 min up to 1 h. After 12th run 3 h, 1 d, 3 d interval spectrum was obtained.

(21) In order to prepare GCMS sample for low boiling material, reaction was run under the standard condition. After 2 h, low boiling cut was collected using dry ice-acetone trap. The sample was analyzed in HP 5890 series II (GC) and HP5971 series MSD (mass detector). Conditions: capillary column DB-wax 30m × 0.25 mm (0.25 μm film thickness), ion source temperature 200 °C, injection temperature 250 °C: oven temperature 35 °C to ca. 240 °C programmed 10 °C/ min, retention time: 2.08 min HCO_2Me, 3.47 min MeOH.

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(27) Methylthio group of quinolinone **1a** was removed by Raney nickel to provide 3-acyl-4-quinolinone (**8**) and acyl group of **1a** was removed by treatment with trifluoro acetic acid as solvent to give 2-methylthio-4-quinolinone (**9**). Reaction of **8** or **9** with MSH did not proceed after overnight stirring under the same condition.