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CYCLIZATION REACTIONS OF 2-ISOTHIOCYANATOPHENYL KETONES GIVING 4-HYDROXYQUINOLINE-2(1*H*)-THIONES AND 4-ALKYLIDENE-1,4-DIHYDRO-3,1-BENZOXAZINE-2-THIONES

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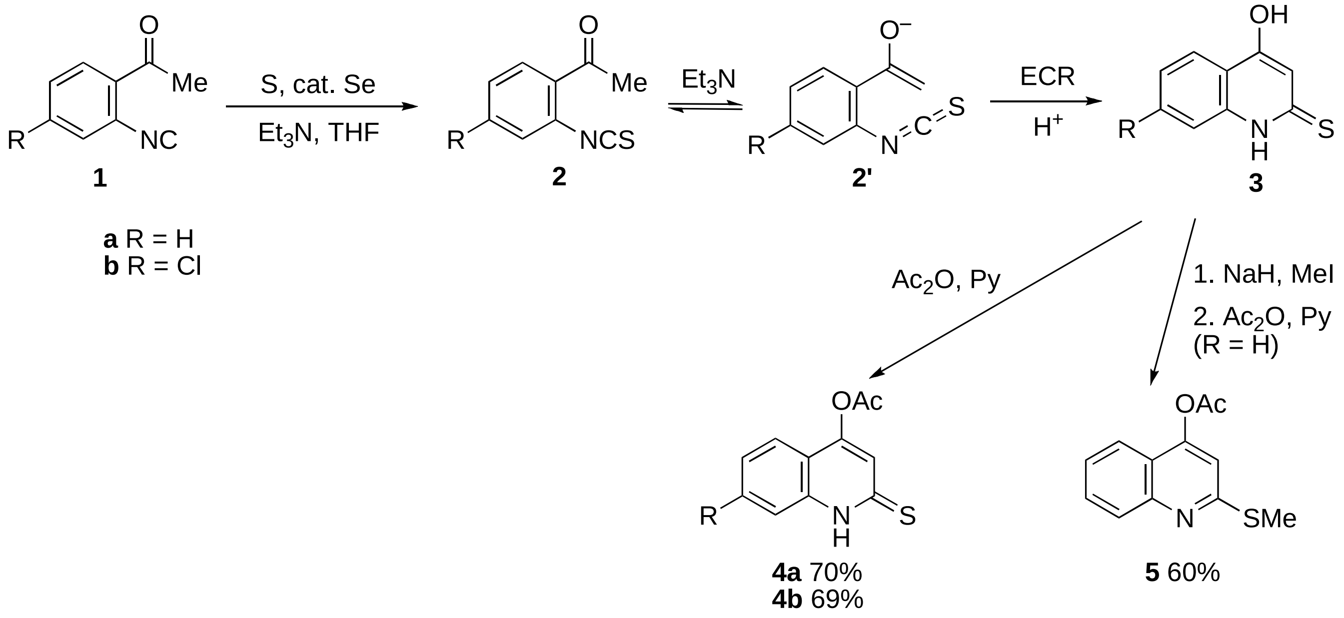
Abstract – 2-Isothiocyanatophenyl methyl ketones, generated in situ by treatment of 2-isocyanophenyl methyl ketones with sulfur in the presence of a catalytic amount of selenium and excess triethylamine, underwent electrocyclic reaction (ECR) via their enolate forms to give 4-hydroxyquinoline-2(1*H*)-thiones. The reaction products from ethyl 2-isothiocyanatophenyl ketones generated in situ from the corresponding isocyanides under similar conditions proved to be the ECR products, 4-hydroxy-3-methylquinoline-2(1*H*)-thiones and/or the ionic cyclization products, 4-ethylidene-1,4-dihydro-3,1-benzoxazine-2-thiones.

INTRODUCTION

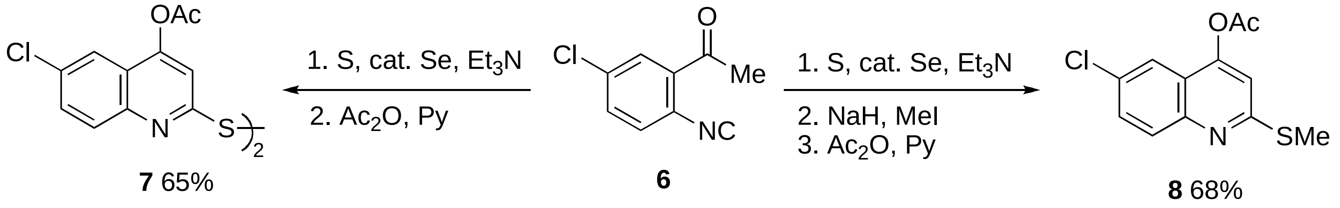
We recently reported that α-substituted 2-isothiocyanatostyrenes, generated in situ by the treatment of the corresponding isocyanides with sulfur in the presence of a catalytic amount of selenium and excess triethylamine under Fujiwara's conditions,[1] underwent ECR to afford 4-substituted quinoline-2(1*H*)-thiones.[2] As an extension of this sequence, we envisaged that the enolate forms of 2-isocyanatophenyl ketones would underwent ECR to give 4-hydroxyquinoline-2(1*H*)-thiones. In this report, we present the results of our investigation on reactivity of 2-isothiocyanatophenyl methyl ketones and ethyl 2-isothiocyanatophenyl ketones. The investigation has indicated that 2-isothiocyanatophenyl methyl ketones, derived from 2-isocyanophenyl methyl ketones, give the corresponding ECR products, 4-hydroxyquinoline-2(1*H*)-thiones, via their enolate forms, and that ethyl 2-isothiocyanatophenyl ketones gave ECR products, 4-hydroxy-3-methylquinoline-2(1*H*)-thiones, along with the ionic cyclization products, 4-ethylidene-1,4-dihydro-3,1-benzoxazine-2-thiones.

RESULTS AND DISCUSSION

It was found that when 2-isocyanophenyl methyl ketone (**1a**) or 4-chloro-2-isocyanophenyl methyl ketone (**1b**) was allowed to react with sulfur in THF containing an excess amount of triethylamine[1] and a catalytic amount of selenium at room temperature, the corresponding 4-hydroxyquinoline-2(1*H*)-thiones (**3**) were formed as shown in Scheme 1. Thus, isocyano ketones **1** were first converted into the corresponding isothiocyanates (**2**). Their enolate forms (**2'**) underwent ECR to produce **3**, which were isolated as their acetates (**4**) in relatively good yields on treatment with acetic acid in pyridine. On the other hand, deprotonation of the thioamide hydrogen of **3a** with an equimolar amount of sodium hydride and subsequent *S*-methylation with iodomethane proceeded smoothly to afford 4-hydroxy-2-methylsulfanylquinoline, which was isolated as 4-acetoxy-2-methylsulfanylquinoline (**5**) on treatment with acetic acid in pyridine in fair yield.



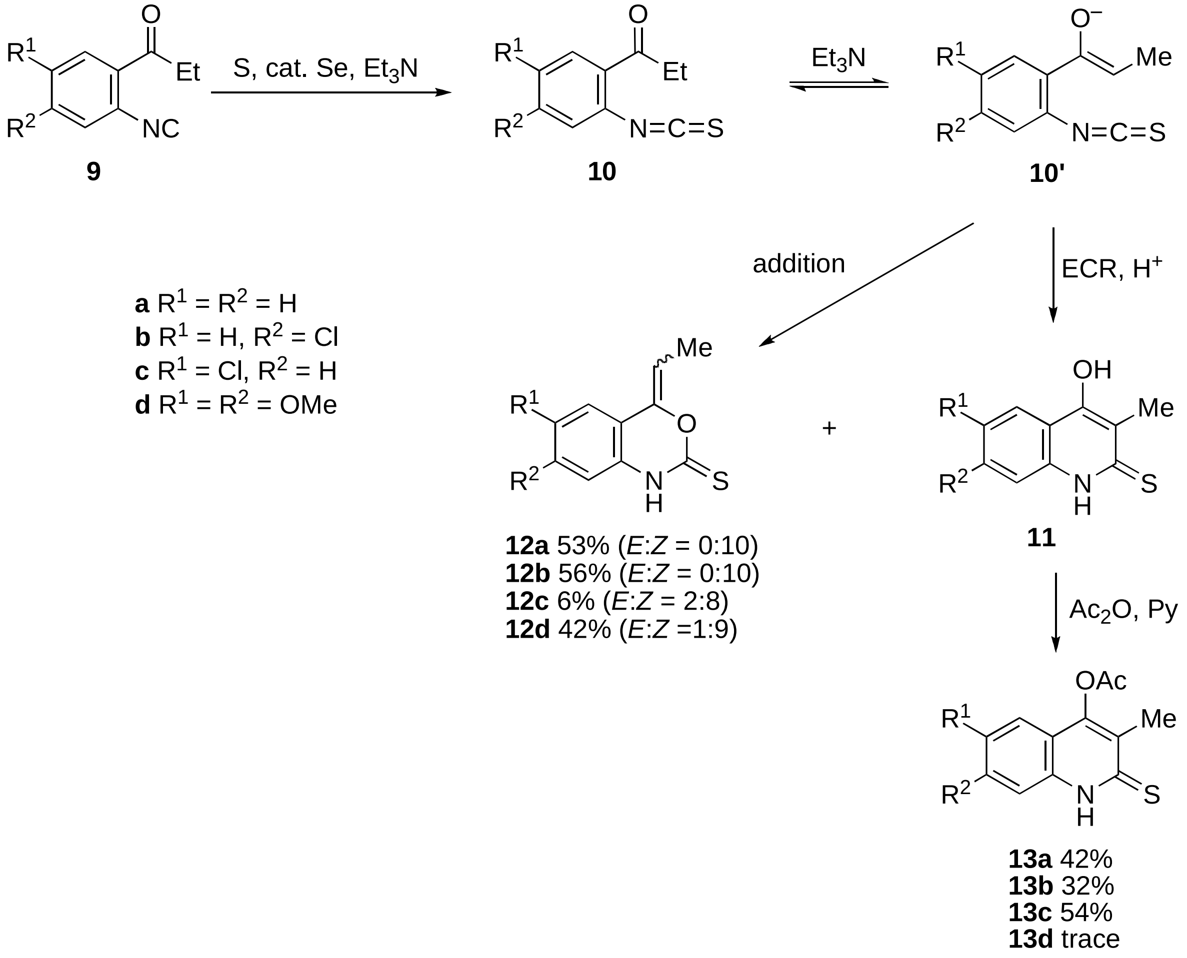
Scheme 1



Scheme 2

Similar treatment of 5-chloro-2-isocyanophenyl methyl ketone (**6**) with sulfur, followed by acetylation of the resulting product as described above produced bis(4-acetoxy-6-chloroquinolin-2-yl) disulfide (**7**) in fair yield. It implies that initially formed 6-chloro-4-hydroxyquinoline-2(1*H*)-thione equilibrates to

6-chloro-2-sulfanylquinolin-4-ol, which is liable to oxidation during *O*-acetylation and/or isolation procedures. However, after treatment of **6** with sulfur, 6-chloro-4-hydroxyquinoline-2(1*H*)-thione was *S*-methylated and *O*-acetylated as described above for the preparation of **5** to give 4-acetoxy-6-chloro-2-methylsulfanylquinoline (**8**) in fair yield. These results are depicted in Scheme 2.



Scheme 3

Subsequently, four ethyl 2-isocyanophenyl ketones (**9**) were prepared and reactivity of the corresponding isothiocyanates **10** was investigated. First, ethyl 2-isocyanophenyl ketone (**9a**) was subjected to the treatment with sulfur under the same conditions as described above. The ECR product (**11a**) was formed via the enolate form (**10a'**) of ethyl 2-isothiocyanatophenyl ketone (**10a**) and isolated as its *O*-acetylated product (**13a**) in 42% yield. However, (*Z*)-4-ethylidene-1,4-dihydro-3,1-benzoxazine-2-thione (**12a**), the product arising from ionic cyclization of **10a**, was also isolated in 53% yield. The less favorable formation of the ECR products from ethyl 2-isothiocyanatophenyl ketones may be due to the effect of the β-methyl group of the intermediates (**10a'**). The stereochemical assignment for **12a** was made on the basis of NOE experiments. Thus, irradiation of the signal at δ 6.22 assignable to the vinyl proton resulted in an enhancement (10%) of the signal at δ 6.86 assignable to 5-H. A similar result was obtained from 4-chloro-2-isothiocyanatophenyl ethyl ketone (**10b**), derived from 4-chloro-2-isocyanophenyl ethyl ketone (**9b**). The ECR product **11b** was isolated as its *O*-acetylated product (**13b**) in 32% yield, along with the corresponding ionic cyclization product (**12b**) in 56% yield as the sole stereoisomer. The stereochemistry of **12b** was determined in a manner similar to that described for **12a**. A similar sequence starting with 5-chloro-2-isocyanophenyl ethyl ketone (**9c**) afforded the ECR product (**13c**) in 54% yield along with small quantity (6%) of a stereoisomeric mixture of the ionic cyclization product (**12c**). This lower yield of **12c** may be ascribed to the electron-withdrawing 5-chloro substituent, which decreases electron density of the carbonyl oxygen. The treatment of ethyl 2-isocyano-4,5-dimethoxyphenyl ketone (**9d**) with sulfur as described above, followed by *O*-acetylation, gave a stereoisomeric mixture of the ionic cyclization product (**12d**) in 42% yield as the sole isolated product; in this reaction only a trace amount of **13d** was obtained as a mixture with products, whose structure could not be well-established. Almost exclusive formation of **12d** may be due to the electron-donating property of the methoxy substituents, which increase electron density of the carbonyl oxygen. The ratios of these stereoisomers were determined by analyses of their ^{1}H NMR spectra. These results are depicted in Scheme 3.

The foregoing results have indicated that 2-isothiocyanatophenyl methyl ketones undergo ECR via their enolate forms in the presence of triethylamine to give 4-hydroxyquinoline-2(1*H*)-thiones exclusively and that ethyl 2-isothiocyanatophenyl ketones afford the corresponding ECR products, 4-hydroxy-3-methylquinoline-2(1*H*)-thiones, along with the ionic cyclization products, 4-ethylene-1,4-dihydro-3,1-benzoxazine-2-thiones. There have been a few method for the preparation of 4-hydroxyquinoline-2(1*H*)-thiones.[3,4] Moreover, there has been only one report on the synthesis of 4-alkylidene-1,4-dihydro-3,1-benzoxazine-2-thiones.[5] The procedure described here should be of use in synthesizing these classes of heterocycles because of the ease of preparation of the starting materials and the simplicity of operations.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined as KBr disks with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were determined using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) m were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF$_{254}$. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 2-Isocyanophenyl ketones (**1a**),[6b] (**6**),[6b] and (**9**),[6b] and 1-(2-amino-4-chlorophenyl)ethanone[7] were prepared by previously reported procedures. All other chemicals used in this study were commercially available.

***N*-(2-acetyl-5-chlorophenyl)formamide.** This compound was prepared by *N*-formylation of 1-(2-amino-4-chlorophenyl)ethanone[7] with formic acid in refluxing toluene in 65% yield; a white solid; mp 115–117 ˚C (hexane–Et_2O); IR 3449, 1694, 1651, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (s, 3H), 7.14 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 8.50 (s, 1H), 8.86 (s, 1H), 11.68 (br s, 1H). Anal. Calcd for $C_9H_8ClNO_2$: 54.70; H, 4.08; N, 7.09. Found: C, 54.64; H, 4.26; N, 6.86.

1-(4-Chloro-2-isocyanophenyl)ethanone (1b). This compound was prepared by treating *N*-(2-acetyl-5-chlorophenyl)formamide with $POCl_3$ in the presence of Et_3N in THF at 0 ˚C in 91% yield and used in the next step without any purification after the usual workup; a beige solid; mp 34–37 ˚C; IR 2131, 1690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71 (s, 3H), 7.47–7.49 (m, 2H), 7.76 (d, *J* = 8.2 Hz, 1H).

Typical Procedure for the Preparation of Products 4, 7, 12, and 13. 2-Thioxo-1,2-dihydroquinolin-4-yl Acetate (4a). A solution of 1-(2-isocyanophenyl)ethanone (**1a**) (0.14 g, 0.95 mmol) in THF (2 mL) containing Et_3N (0.25 g, 2.5 mmol), sulfur (38 mg, 1.2 mmol), and selenium (2.3 mg, 0.029 mmol) was stirred overnight at rt. Then, THF and Et_3N were removed by evaporation to give a residue and pyridine and Ac_2O (0.5 mL each) was added to it. After stirring for 2 h, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (1:2 THF–hexane) to give **4a** (0.15 g, 70%); a yellow solid; mp 188–191 ˚C (decomp) (hexane–THF); IR 3449, 1775, 1622, 1184 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.35 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.42 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.61 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 12.15 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.87, 116.39, 117.79, 122.30, 122.42, 124.37, 132.15, 140.37, 151.89, 168.02, 181.67; MS *m/z* 219 (M$^+$, 37), 177 (100). Anal. Calcd for $C_{11}H_9NO_2S$; C, 60.26; H, 4.14; N, 6.39. Found: C, 60.25; H, 4.17; N, 6.37.

7-Chloro-2-thioxo-1,2-dihydroquinolin-4-yl Acetate (4b): a yellow solid; mp 211–214 ˚C (decomp) (hexane–THF); IR 3455, 1767, 1631, 1196 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.36 (s, 3H), 7.15 (s, 1H), 7.34 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 12.37 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.87, 115.56, 116.66, 122.63, 124.13, 124.45, 127.59, 140.90, 151.37, 167.83, 171.90. Anal. Calcd for $C_{11}H_8ClNO_2S$; C, 52.08; H, 3.18; N, 5.52. Found: C, 52.03; H, 3.21; N, 5.40.

6-Chloro-2-(4-acetoxy-6-chloroquinolin-2-yldisulfanyl)quinolin-4-yl Acetate (7): an orange solid; mp 189–192 ˚C (decomp) (hexane–THF); IR 1773, 1663, 1185 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 6H), 7.65 (dd, *J* = 8.8, 1.9 Hz, 2H), 7.72 (s, 2H), 7.83 (d, *J* = 1.9 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.07, 110.22, 120.51, 121.59, 130.15, 131.81, 132.65, 147.93, 154.06, 159.96, 167.50; MS *m/z* 504 (M$^+$, 30), 462 (100). Anal. Calcd for $C_{22}H_{14}Cl_2N_2O_4S_2$; C, 52.28; H, 2.79; N, 5.54.

Found: C, 52.21; H, 2.71; N, 5.41.

(*Z*)-4-Ethylidene-1,4-dihydrobenz-3,1-oxazine-2-thione (12a): a white solid; mp 178–182 °C (THF); IR 3181, 1655 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.92 (d, *J* = 6.9 Hz, 3H), 6.22 (q, *J* = 6.9 Hz, 1H), 6.86 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.10 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.26 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.44 (dd, *J* = 7.8, 0.9 Hz, 1H), 8.72 (br s, 1H); MS *m/z* 191 (M$^+$, 100). Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: 62.58; H, 4.68; N, 7.26.

3-Methyl-2-thioxo-1,2-dihydroquinolin-4-yl Acetate (13a): a yellow solid; mp 223–225 °C (decomp) (hexane–THF); IR 1769, 1630, 1188 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.42 (s, 3H), 7.29 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 11.78 (br s, 1H); MS *m/z* 233 (M$^+$, 43), 191 (100). Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: 61.63; H, 4.71; N, 5.95.

(*Z*)-7-Chloro-4-ethylidene-1,4-dihydrobenz-3,1-oxazine-2-thione (12b): a pale-yellow solid; mp 200–203 °C (decomp) (hexane–THF); IR 3177, 1670, 1614 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (d, *J* = 6.9 Hz, 3H), 6.20 (q, *J* = 6.9 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 7.07 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 8.81 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.67, 117.33, 119.34, 124.16, 124.50, 125.06, 125.78, 134.92, 136.48, 167.00; MS *m/z* 225 (M$^+$, 100). Anal. Calcd for $C_{10}H_8ClNOS$: C, 53.22; H, 3.57; N, 6.21. Found: 53.22; H, 3.73; N, 5.94.

7-Chloro-3-methyl-2-thioxo-1,2-dihydroquinolin-4-yl Acetate (13b): a pale-yellow solid; mp 218–221 °C (decomp) (hexane–THF); IR 3453, 1765, 1632, 1192 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.10 (s, 3H), 2.44 (s, 3H), 7.59–7.60 (m, 2H), 7.71 (s, 1H), 11.86 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.89, 20.46, 118.10, 119.27, 121.22, 128.79, 129.32, 131.23, 136.99, 148.70, 167.87, 182.95. Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76; N, 5.23. Found: 53.58; H, 3.79; N, 5.25.

6-Chloro-4-ethylidene-1,4-dihydrobenz-3,1-oxazine-2-thione (12c): a mixture of stereoisomers (*E*:*Z* = *ca*. 2:8); a yellow solid; mp 180–190 °C; IR 3174, 1674, 1615 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.85 (d, *J* = 7.3 Hz, 2.4H), 1.93 (d, *J* = 7.3 Hz, 0.6H), 6.01 (q, *J* = 7.3 Hz, 0.2H), 6.16 (q, *J* = 7.3 Hz, 0.8H), 6.78 (d, *J* = 8.2 Hz, 0.8H), 6.85 (d, *J* = 8.7 Hz, 0.2H), 7.15 (dd, *J* = 8.2, 2.3 Hz, 0.8H), 7.20 (dd, *J* = 8.7, 2.3 Hz, 0.2H), 7.29 (d, *J* = 2.3 Hz, 0.2H), 7.34 (d, *J* = 2.3 Hz, 0.8 H), 9.18 (br s, 0.2H), 9.26 (br s, 0.8H); MS *m/z* 225 (M$^+$, 100). Anal. Calcd for $C_{10}H_8ClNOS$: C, 53.22; H, 3.57; N, 6.21. Found: 52.93; H, 3.54; N, 6.14.

6-Chloro-3-methyl-2-thioxo-1,2-dihydroquinolin-4-yl Acetate (13c): a yellow solid; mp 255–258 °C (decomp) (hexane–THF); IR 3449, 1761, 1201 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.49 (s, 3H), 7.30 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.47 (d, *J* = 1.8 Hz, 1H), 11.80 (br , 1H); MS *m/z* 267 (M$^+$, 35), 255 (100). Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76; N, 5.23. Found: 53.66; H, 3.90; N, 5.13.

4-Ethylidene-6,7-dimethoxy-1,4-dihydrobenz-3,1-oxazine-2-thione (12d): a mixture of stereoisomers

(*E*:*Z* = *ca*. 1:9); a pale-yellow solid; mp 205–214 ˚C; IR 3179, 1655, 1611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (d, *J* = 6.9 Hz, 2.7H), 2.01 (d, *J* = 7.3 Hz, 0.3H), 3.88 (s, 0.3H), 3.89 (s, 2.7H), 3.90 (s, 2.7H), 3.91 (s, 0.3H), 5.92 (q, *J* = 7.3 Hz, 0.1H), 6.08 (q, *J* = 6.9 Hz, 0.9H), 6.36 (s, 0.9H), 6.46 (s, 0.1H), 6.90 (s, 0.9H), 6.98 (s, 0.1H), 8.68 (br s, 0.1H), 8.76 (br s, 0.9H); MS *m/z* 251 (M$^+$, 100). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: 57.11; H, 5.40; N, 5.28.

2-(Methylsulfanyl)quinolin-4-yl Acetate (5). A solution of 1-(2-isocyanophenyl)ethanone (**1a**) (0.19 g, 1.3 mmol) in THF (3 mL) containing Et_3N (0.33 g, 3.3 mmol), sulfur (50 mg, 1.6 mmol), and selenium (3.0 mg, 0.039 mmol) was stirred overnight at rt. Then, the mixture was cooled down to 0 ˚C, and NaH (60% in oil; 52 mg, 1.3 mmol) was added to it. After ceasing the evolution of H_2 gas, MeI (0.18 g, 1.3 mmol) was added and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the organic materials were extracted with AcOEt twice (10 mL each). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was purified by preparative TLC on silica gel (1:4 AcOEt–hexane) to give **5** (0.18 g, 60%); colorless crystals; mp 49–52 ˚C (hexane–CH_2Cl_2); IR 1771, 1616, 1211 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.70 (s, 3H), 7.17 (s, 1H), 7.44 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H); MS *m/z* 233 (M$^+$, 30), 191 (100). Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: 61.62; H, 4.82; N, 5.90.

6-Chloro-2-(Methylsulfanyl)quinolin-4-yl Acetate (8). This compound was prepared from 1-(5-chloro-2-isocyanophenyl)ethanone in a similar manner as described for the preparation of **5**; a pale-yellow solid; mp 94–97 ˚C (pentane); IR 1780, 1612, 1184 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.68 (s, 3H), 7.21 (s, 1H), 7.59 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.79 (d, *J* = 2.6 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 13.12, 21.12, 112.69, 120.42, 120.88, 129.64, 130.97, 131.09, 148.10, 151.96, 161.18, 167.71. Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76; N, 5.23. Found: 53.78; H, 3.82; N, 5.12.

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