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SYNTHESIS OF 3-SUBSTITUTED 4-SULFANYL-8-METHOXYISOQUINOLIN-1(2*H*)-ONES BY THE REACTION OF ETHYL 2-[LITHIO(SULFANYL)METHYL]-6-METHOXYBENZOATES WITH ALIPHATIC AND AROMATIC NITRILES

Kazuhiro Kobayashi,* Hiroo Hashimoto, and Kazuhiro Nakagawa

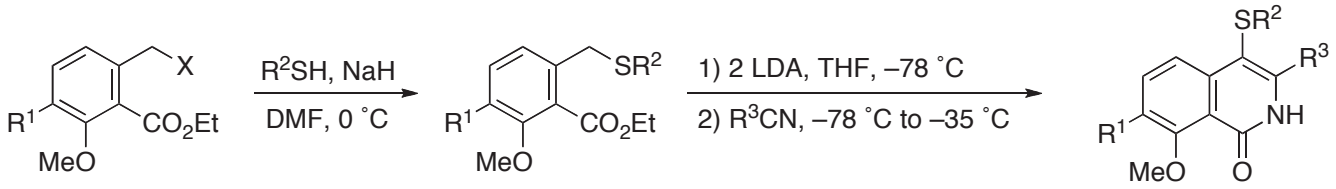
Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan; E-mail: kkoba@chem.tottori-u.ac.jp

Abstract – A convenient method for the synthesis of 3-substituted 4-alkyl(or aryl)sulfanyl-8-methoxyisoquinolin-1(2*H*)-ones has been developed. Ethyl 2-(alkyl(or aryl)sulfanyl)methyl-6-methoxybenzoates, prepared by the reaction of readily available ethyl 2-halomethyl-6-methoxybenzoates with sodium thiolates, are deprotonated on treatment with lithium diisopropylamide (LDA) to generates the corresponding benzyl anions, which react cleanly with a variety of nitriles to provide generally good yields of the corresponding desired isoquinolin-1(2*H*)-ones.

Many compounds having the isoquinolin-1(2*H*)-one unit have shown variety of biological activities.[1] Therefore, development of new routes for the synthesis of isoquinolin-1(2*H*)-ones have recently been extensively explored.[2] However, there have been few reports on the synthesis of 4-(alkyl(or aryl)sulfanyl)isoquinolin-1(2*H*)-ones.[3] This led us to explore a method for preparing this type of isoquinolin-1(2*H*)-ones. We decided to examine the reaction of the benzyl anions of 2-[(alkyl(or aryl)sulfanyl)methyl]benzoates with various nitriles as a quick route to access the required isoquinolin-1(2*H*)-one derivatives. We wish to report here the results of our study, which provide a facile method for the preparation of 3-substituted 4-alkyl(or aryl)sulfanyl-8-methoxyisoquinolin-1(2*H*)-ones.

We first conducted reaction of ethyl 2-(ethylsulfanyl)benzoate with lithium diisopropylamide (LDA) and then benzonitrile. However, it resulted in the formation of a considerably complex mixture of products, from which no more than a trace amount of the desired isoquinolin-1(2*H*)-one derivative was obtained. This result imply that the carbanion generated from ethyl 2-(ethylsulfanyl)benzoate is not enough stable to react the nitrile cleanly. We anticipated that introduction of a methoxy group at the 6-position of 2-(ethylsulfanyl)benzoate should stabilize the benzyl carbanions, because the benzyl anion (**4**) could be

stabilized by its tautomeric form (**4'**) due to the chelation of the lone pair of the methoxy oxygen to the lithium cation (see Scheme 2). 2-(Alkyl(or aryl)sulfanyl)methyl-6-methoxybenzoates (**2a-2d**) were synthesized from 2-halomethyl-6-methoxybenzoates (**1a**[4] and **1b**[5]), easily prepared according to appropriate reported procedures, on treatment with sodium thiolates, generated from the respective thiols and sodium hydride, in good yields as shown in Scheme 1.



1a R^1 = H, X = Br
1b R^1 = OMe, X = Cl

2a R^1 = H, R^2 = Et 89%
2b R^1 = H, R^2 = Ph 89%
2c R^1 = OMe, R^2 = Et 99%
2d R^1 = OMe, R^2 = 4-ClC_6H_4 78%

3

Scheme 1

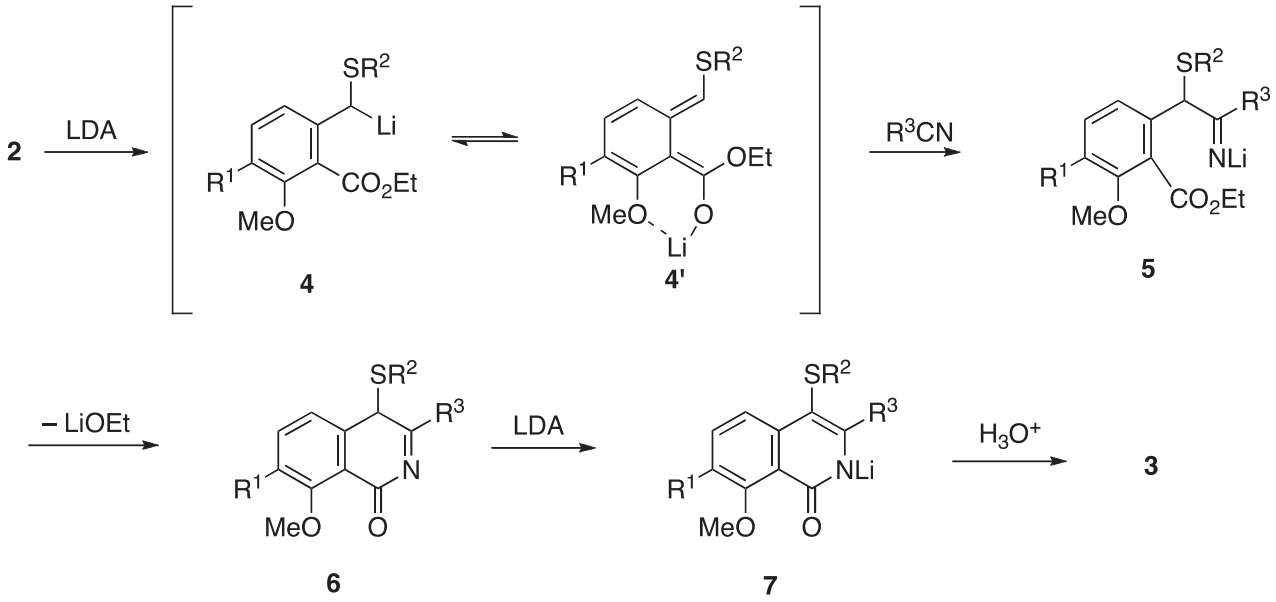
Table 1. Preparation of 3-Substituted 4-alkyl(or aryl)sulfanyl-8-methoxyisoquinolin-1(2*H*)-ones (**3**)

Entry	**2**	R^3	**3**	Yield/%[a]
1	**2a** (R^1 = H, R^2 = Et)	Ph	**3a**	94
2	**2a**	*p*-Tol	**3b**	93
3	**2a**	Et	**3c**	84
4	**2a**	*i*-Pr	**3d**	93
5	**2b** (R^1 = H, R^2 = Ph)	Ph	**3e**	89
6	**2b**	2-ClC_6H_4	**3f**	89
7	**2b**	4-ClC_6H_4	**3g**	86
8	**2c** (R^1 = OMe, R^2 = Et)	Ph	**3h**	67
9	**2c**	2-ClC_6H_4	**3i**	66
10	**2c**	4-ClC_6H_4	**3j**	66
11	**2c**	naphthalen-1-yl	**3k**	67
12	**2d** (R^1 = OMe, R^2 = 4-ClC_6H_4)	Ph	**3l**	80
13	**2d**	3-$MeOC_6H_4$	**3m**	75

[a] Yields of Isolated products.

As expected, 4-ethylsulfanyl-8-methoxy-3-phenylisoquinolin-1(2*H*)-one (**3a**) was obtained by a treatment of **2a** with an equimolar amount of LDA followed by addition of benzonitrile. However yield of **3a** was unsatisfactory (37%). We found that the use of two equivalents of LDA gave the desired product (**3a**) in excellent yield (Table 1, Entry 1). Having obtained this successful result, we examined the scope the present reaction. The results obtained by using three other 2-(alkyl(or aryl)sulfanyl)methyl-6-methoxybenzoates (**2b-d**) and seven other nitriles are also summarized in Table 1. These results indicate that aliphatic nitriles, such as propanenitrile (Entry 3) and 2-methylpropanenitrile (Entry 4), having α-hydrogen(s) can also be employed in this reaction and the corresponding isoquinolin-1(2*H*)-ones (**3c**)

and (**3d**), respectively, can be obtained in satisfactory yields comparable to those using aromatic nitriles. Unfortunately, however, it should be noted that no desired products could be obtained with trichloroacetonitrile and 3-phenylpropenenitrile; the reactions using these nitriles gave considerably complicated mixtures of products. It is also indicated that 2-(alkyl(or aryl)sulfanyl)methyl-5,6-dimethoxybenzoates (**2c**) and (**2d**) undergoes this sequences to afford the corresponding products (Entries 8–13). However, the yields are somewhat lower compared to those from 2-(alkyl(or aryl)sulfanyl)methyl-6-dimethoxybenzoates (**2a**) and (**2b**) (Entries 1–7). This may be attributable to less stability of the carbanions generated from **2c** and **2d** due to the 5-methoxy group.



Scheme 2

Mechanistically, the present reaction leading ethyl 2-(alkyl(or aryl)sulfanyl)methyl-6-methoxybenzoates (**2**) to 3-substituted 4-alkyl(or aryl)sulfanyl-8-methoxyisoquinolin-1(2*H*)-ones (**3**) appears to proceed as illustrated in Scheme 2. The necessity of two equivalents of LDA for the satisfactory production of the desired products may be rationalized by this mechanism. Deprotonation of one of benzyl hydrogens of **2** by the first molar of LDA generates the benzyllithium intermediate (**4**). The benzyl anion attacks on the nitrile carbon to provide the imino lithium intermediate (**5**), which cyclizes to form the isoquinoline-1(4*H*)-one intermediate (**6**). The 4-proton of this intermediate was then abstracted by the second molar of LDA to give 2-lithioisoquinolin-2-(1*H*)-one intermediate (**7**), which was protonated to give **3**.

In conclusion, we have demonstrated that the procedure mentioned above allows us to obtain 3-substituted 8-methoxy-4-sulfanylisoquinolin-1(2*H*)-ones. Since the starting materials are readily available and the operations are very simple, the present method offers a very convenient route to this type of isoquinolinones.

EXPERIMENTAL

The melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. Ethyl 2-halomethyl-6-methoxybenzoates **1a**[4] and **1b**[5] were prepared according to the appropriate reported procedures. *n*-BuLi was supplied by Asia Lithium Corporation. All of the other chemicals used in this study were commercially available.

Ethyl 2-Alkyl(or aryl)sulfanylmethyl-6-methoxybenzoates (2). These sulfenylated esters were prepared by treating **1** with the respective sodium thiolates, generate in situ from thiols and NaH, in DMF at 0 ˚C.

Ethyl 2-Ethylsulfanylmethyl-6-methoxybenzoate (2a): a pale-yellow liquid; R_f 0.44 (1:3 Et_2O–hexane); IR (neat) 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.3 Hz, 3H), 1.39 (t, J = 7.3 Hz, 3H), 2.44 (q, J = 7.3 Hz, 2H), 3.74 (s, 2H), 3.83 (s, 3H), 4.41 (q, J = 7.3 Hz, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 7.29 (dd, J = 8.2, 7.8 Hz, 1H). Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13. Found: C, 61.29; H, 7.14.

Ethyl 2-Methoxy-6-phenylsulfanylmethylbenzoate (2b): a yellow oil; R_f 0.43 (1:2 Et_2O–hexane); IR (neat) 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.3 Hz, 3H), 3.83 (s, 3H), 4.14 (s, 2H), 4.39 (q, J = 7.3 Hz, 2H), 6.82 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 7.17 (tt, J = 7.3, 1.4 Hz, 1H), 7.21–7.26 (m, 3H), 7.30 (dd, J = 7.8, 1.4 Hz, 2H). Anal. Calcd for $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00. Found: C, 67.51; H, 6.06.

Ethyl 2-Ethyllsulfanylmethyl-2,3-dimethoxybenzoate (2c): a colorless liquid; R_f 0.57 (1:3 AcOEt–hexane); IR (neat) 1724, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.3 Hz, 3H), 1.40 (t, J = 7.3 Hz, 3H), 2.44 (q, J = 7.3 Hz, 2H), 3.72 (s, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.41 (q, J = 7.3 Hz, 2H), 6.88 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H). Anal. Calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09. Found: C, 59.09; H, 7.04.

Ethyl 2-(4-Chlorophenylsulfanylmethyl)-2,3-dimethoxybenzoate (2d): a colorless oil; R_f 0.39 (1:5 AcOEt–hexane); IR (neat) 1724, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.3 Hz, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.09 (s, 2H), 4.39 (q, J = 7.3 Hz, 2H), 6.82 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 8.7 Hz, 1H), 7.21 (s, 4H). Anal. Calcd for $C_{18}H_{19}ClO_4S$: C, 58.93; H, 5.22. Found: C, 58.79; H, 5.40.

General Procedure for the Preparation of Isoquinolin-1(2*H*)-ones (3). To a stirred solution of LDA (2.0

mmol), generated from *n*-BuLi and *i*-Pr_2NH by the standard procedure, in THF (5 mL) at –78 ˚C was added **2** (1.0 mmol); the mixture turned deep red immediately. After 15 min, one of the nitriles (1.0 mmol) was added and the temperature was raised gradually until characteristic red color faded (approximately –35 ˚C). The reaction was quenched by adding saturated aqueous NH_4Cl (20 mL), and the organic materials were extracted with Et_2O three times (10 mL each). The combined extracts were washed with water and then brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residual solid was recrystallized from an appropriate solvent to give pure **3**.

4-Ethylsulfanyl-8-methoxy-3-phenylisoquinolin-1(2*H*)-one (3a): a white solid; mp 198–202 ˚C (hexane–CH_2Cl_2); IR (KBr) 3161, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H), 2.49 (q, *J* = 7.3 Hz, 2H), 4.03 (s, 3H), 6.98 (d, *J* = 8.2 Hz, 1H), 7.48–7.53 (m, 5H), 7.69 (t, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 8.54 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.16, 29.74, 56.37, 106.91, 108.61, 115.12, 118.27, 128.27, 129.36, 129.41, 133.78, 135.50, 142.32, 146.24, 160.88, 161.29; MS *m/z* 311 (M^+, 100). Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.19; H, 5.53; N, 4.52.

4-Ethylsulfanyl-8-methoxy-3-(4-methylphenyl)isoquinolin-1(2*H*)-one (3b): a white solid; mp 169–171 ˚C (hexane–CH_2Cl_2); IR (KBr) 3163, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H), 2.43 (s, 3H), 2.49 (q, *J* = 7.3 Hz, 2H), 4.03 (s, 3H), 6.97 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.68 (t, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 8.40 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.16, 29.72, 34.21, 56.39, 106.73, 108.49, 115.05, 118.27, 129.01, 129.16, 132.68, 133.76, 139.58, 142.39, 146.27, 160.83, 161.38; MS *m/z* 325 (M^+, 100). Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 70.12; H, 5.88; N, 4.30. Found: C, 70.08; H, 5.98; N, 4.22.

3-Ethyl-4-ethylsulfanyl-8-methoxyisoquinolin-1(2*H*)-one (3c): a white solid; mp 176–179 ˚C (hexane–CH_2Cl_2); IR (KBr) 3161, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (t, *J* = 7.3 Hz, 3H), 1.31 (t, *J* = 7.3 Hz, 3H), 2.65 (q, *J* = 7.3 Hz, 2H), 3.02 (q, *J* = 7.3 Hz, 2H), 4.00 (s, 3H), 6.90 (d, *J* = 8.2 Hz, 1H), 7.62 (t, *J* = 8.2 Hz, 1H), 7.93 (dd, *J* = 8.2, 0.9 Hz, 1H), 8.04 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.43, 14.49, 26.43, 29.71, 56.34, 105.52, 107.83, 114.72, 117.81, 133.51, 142.62, 149.49, 161.32, 162.01; MS *m/z* 263 (M^+, 100). Anal. Calcd for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.82; H, 6.81; N, 5.29.

4-Ethylsulfanyl-8-methoxy-3-(1-methylethyl)isoquinolin-1(2*H*)-one (3d): a white solid; mp 168–171 ˚C (hexane–CH_2Cl_2); IR (KBr) 3179, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, *J* = 7.3 Hz, 3H), 1.31 (d, *J* = 6.9 Hz, 6H), 2.65 (q, *J* = 7.3 Hz, 2H), 4.01 (s, 3H), 4.18 (septet, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 7.64 (t, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 8.82 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.50, 21.02, 29.67, 30.19, 56.34, 104.68, 107.90, 114.70, 118.12, 133.52, 142.47, 152,13, 161.30, 161.55; MS *m/z* 277 (M^+, 82), 248 (100). Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05. Found: C, 64.93; H, 6.96; N, 5.03.

8-Methoxy-3-phenyl-4-phenylsulfanylisoquinolin-1(2*H*)-one (3e): a white solid; mp 244–247 ˚C (hexane–CH_2Cl_2); IR (KBr) 3156, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (s, 3H), 6.97 (d, *J* = 8.2 Hz, 1H),

7.02 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 7.19 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.39–7.58 (m, 5H), 7.56 (t, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 8.64 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.38, 103.68, 108.95, 115.12, 118.30, 125.00, 125.43, 128.42, 128.53, 128.98, 129.80, 134.21, 134.93, 138.37, 141.71, 147.75, 161.01, 161.30; MS *m/z* 359 (M^+, 100). Anal. Calcd for $C_{22}H_{17}NO_2S$: C, 73.51; H, 4.77; N, 3.90. Found: C, 73.48; H, 4.79; N, 3.82.

3-(2-Chlorophenyl)-8-methoxy-4-phenylsulfanylisoquinolin-1(2*H*)-one (3f): a white solid; mp 207–210 °C (hexane–CH_2Cl_2); IR (KBr) 3190, 1655, 1642, 1611 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H), 6.99 (dd, *J* = 7.3, 0.9 Hz, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 2H), 7.32 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.40–7.44 (m, 2H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.59 (dd, *J* = 8.2, 7.8 Hz, 1H), 11.68 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 56.04, 102.29, 109.53, 115.33, 116.97, 125.08, 125.37, 126.82, 129.02, 129.10, 130.62, 130.82, 132.40, 133.85, 133.94, 137.09, 140.37, 146.86, 159.98, 160.92; MS *m/z* 393 (M^+, 100). Anal. Calcd for $C_{22}H_{16}ClNO_2S$: C, 67.08; H, 4.09; N, 3.56. Found: C, 67.04; H, 4.10; N, 3.56.

3-(4-Chlorophenyl)-8-methoxy-4-phenylsulfanylisoquinolin-1(2*H*)-one (3g): a white solid; mp 253–256 °C (hexane–CH_2Cl_2); IR (KBr) 3161, 1665 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H), 6.98 (dd, *J* = 7.3, 1.4 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.42 (d, *J* = 9.2 Hz, 2H), 7.45 (d, *J* = 9.2 Hz, 2H), 7.52 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.58 (t, *J* = 8.2 Hz, 1H), 11.59 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 56.04, 101.06, 109.40, 115.17, 117.03, 125.01, 125.09, 127.85, 129.23, 130.94, 133.37, 133.98, 134.01, 137.71, 140.71, 148.62, 160.07, 160.88; MS *m/z* 393 (M^+, 100). Anal. Calcd for $C_{22}H_{16}ClNO_2S$: C, 67.08; H, 4.09; N, 3.56. Found: C, 67.07; H, 4.16; N, 3.54.

4-Ethylsulfanyl-7,8-dimethoxy-3-phenylisoquinolin-1(2*H*)-one (3h): a white solid; mp 163–166 °C (hexane–Et_2O); IR (KBr) 3158, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H), 2.48 (q, *J* = 7.3 Hz, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.47–7.53 (m, 5H), 8.20 (d, *J* = 8.7 Hz, 1H), 8.79 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.23, 29.79, 56.64, 61.68, 106.78, 118.82, 120.40, 122.33, 128.22, 129.18, 129.52, 134.28, 135.57, 143.84, 149.79, 151.67, 160.77; MS *m/z* 341 (M^+, 100). Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.72; H, 5.81; N, 4.02.

3-(2-Chlorophenyl)-4-ethylsulfanyl-7,8-dimethoxyisoquinolin-1(2*H*)-one (3i): a white solid; mp 193–194 °C (hexane–CH_2Cl_2); IR (KBr) 3156, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (t, *J* = 7.3 Hz, 3H), 2.53 (q, *J* = 7.3 Hz, 2H), 3.91 (s, 3H), 3.98 (s, 3H), 7.36–7.44 (m, 4H), 7.51 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 9.05 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.48, 29.64, 56.61, 61.66, 108.50, 118.65, 120.70, 122.27, 126.58, 129.67, 130.50, 131.75, 133.68, 133.92, 134.46, 141.20, 149.80, 151.93, 161.06; MS *m/z* 375 (M^+, 100). Anal. Calcd for $C_{19}H_{18}ClNO_3S$: C, 60.71; H, 4.83; N, 3.73. Found: C, 60.49; H, 4.87; N, 3.62.

3-(4-Chlorophenyl)-4-ethylsulfanyl-7,8-dimethoxyisoquinolin-1(2*H*)-one (3j): a pale-yellow solid; mp 202–205 °C (hexane–$CHCl_3$); IR (KBr) 3156, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H),

2.47 (q, *J* = 7.3 Hz, 2H), 3.87 (s, 3H), 3.98 (s, 3H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 8.19 (d, *J* = 8.7 Hz, 1H), 9.51 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.22, 29.82, 56.60, 61.51, 107.22, 118.82, 120.43, 122.36, 128.39, 131.18, 133.83, 134.07, 135.17, 142.85, 149.71, 151.80, 161.25; MS *m/z* 375 (M^+, 100). Anal. Calcd for $C_{19}H_{18}ClNO_3S$: C, 60.71; H, 4.83; N, 3.73. Found: C, 60.41; H, 5.00; N, 3.51.

4-Ethylsulfanyl-7,8-dimethoxy-3-(naphthalen-1-yl)isoquinolin-1(2*H*)-one (3k): a pale-yellow solid; mp 198–201 °C (hexane–$CHCl_3$); IR (KBr) 3148, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3H), 2.39–2.51 (m, 2H), 3.94 (s, 3H), 4.00 (s, 3H), 7.46–7.59 (m, 5H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 8.19 (d, *J* = 8.7 Hz, 1H), 8.69 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.34, 29.87, 56.63, 61.62, 108.77, 118.75, 120.64, 122.20, 124.98, 125.09, 126.32, 126.92, 127.70, 128.48, 129.72, 131.36, 133.04, 133.41, 134.02, 142.19, 149.86, 151.86, 160.66; MS *m/z* 391 (M^+, 100). Anal. Calcd for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.37; H, 5.47; N, 3.30.

4-(4-Chlorophenylsulfanyl)-7,8-dimethoxy-3-phenylisoquinolin-1(2*H*)-one (3l): a white solid; mp 265–268 °C (hexane–CH_2Cl_2); IR (KBr) 3160, 1653, 1607 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 3H), 3.83 (s, 3H), 7.02 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.37–7.43 (m, 5H), 7.51 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 11.43 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 56.25, 60.58, 114.64, 119.32, 120.75, 126.67, 127.38, 128.60, 128.66, 129.40, 134.36, 136.84, 136.89, 144.64, 146.83, 151.21, 159.39, 163.57, 164.12; MS *m/z* 423 (M^+, 100). Anal. Calcd for $C_{23}H_{18}ClNO_3S$: C, 65.17; H, 4.28; N, 3.30. Found: C, 65.08; H, 4.29; N, 3.18.

4-(4-Chlorophenylsulfanyl)-7,8-dimethoxy-3-(3-methoxyphenyl)isoquinolin-1(2*H*)-one (3m): a white solid; mp 226–229 °C (hexane–CH_2Cl_2); IR (KBr) 3196, 1659 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.66 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 6.95–6.98 (m, 3H), 7.04 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.29 (dd, *J* = 8.2, 7.9 Hz, 1H), 7.51 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 11.51 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 54.99, 56.13, 60.87, 100.21, 112.78, 114.46, 114.88, 119.01, 120.44, 121.19, 126.72, 128.97, 129.07, 129.47, 132.17, 136.13, 137.36, 148.73, 151.40, 158.30, 158.45, 159.82; MS *m/z* 453 (M^+, 100). Anal. Calcd for $C_{24}H_{20}ClNO_4S$: C, 63.50; H, 4.44; N, 3.09. Found: C, 63.42; H, 4.48; N, 3.03.

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