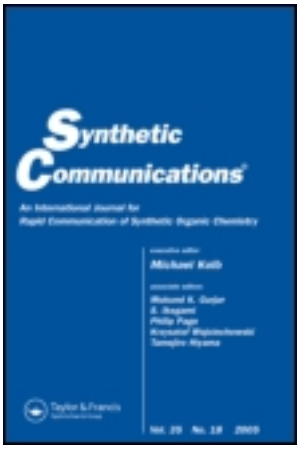

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[Omim][NO_3], a Green and Base-Free Medium for One-Pot Synthesis of Benzothiazinones at Room Temperature

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[Omim][NO_3], A GREEN AND BASE-FREE MEDIUM FOR ONE-POT SYNTHESIS OF BENZOTHIAZINONES AT ROOM TEMPERATURE

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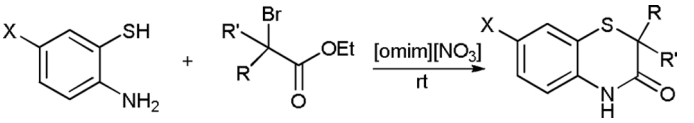
Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran

GRAPHICAL ABSTRACT



Abstract *A general and efficient room-temperature procedure is developed for high-yield synthesis of 2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one derivatives in one pot from the reaction of 2-aminothiophenols with 2-bromoalkanoates in ionic liquid [bmim]NO_3 without the use of any catalyst, base, or additive. Products were obtained in good yields by simple extraction with Et_2O followed by evaporation of the volatile contents and recrystallization from Et_2O. The ionic liquid was recycled and reused in the next reaction without the loss of its activity.*

Keywords 1,4-Benzothiazin-3-ones; green chemistry; heterocyclization; ionic liquids

INTRODUCTION

Along with the worldwide increase in environmental safety enforcement, ionic liquids (ILs) have been recognized as useful green media in various fields of chemistry.[1] In particular, chemists can tailor ILs with desired physical and chemical properties to boost the selectivity and reactivity of various synthetic transformations.[2] Consequently, ILs are known nowadays as environmentally benign surrogates for conventional organic solvents because they are easily recoverable, have very low vapor pressure, exhibit increased thermal stability, are able to dissolve a wide range of organic compounds, and possess long shelf lives.[3]

The 2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (**3**) structural motif is characteristic of a very important class of heterocyclic compounds possessing significant pharmaceutical and biological properties.[4] Moreover, their industrial[5] and agricultural[6] applications are also significant. As a result, are currently devoting synthetic chemists extensive efforts to develop more efficient and simpler methods for the synthesis of these heterocycles.

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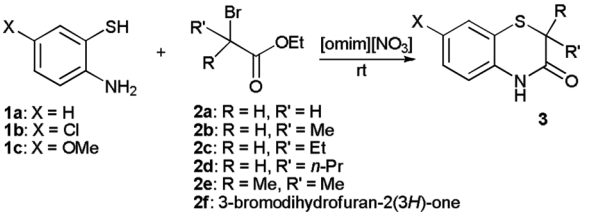
Several routs have been offered so far for the synthesis of benzothiazin-3-ones, such as cyclization of o-aminothiophenols or their disulfide equivalents with appropriately α-substituted carbonyl compounds,[7] replacement of the halogen atom of halonitrobenzenes with a thiol acetate followed by the reduction of the nitro group prior to the final annulation step,[8] and the reaction of 2-chloroanilines with sodium sulfide and then cyclization of the aminothiophenol intermediate with chloroacetic acid derivatives.[9] Other methods are based on the Smiles rearrangement, which involves a one-pot reaction of 2-chlorothiophenols with chloroacetyl chlorides and amines,[10] and ring expansion of appropriate smaller heterocycles.[11] Nevertheless, many of the reported methods involve more than one-step reactions, require heating at high temperatures, do not produce good yields of diverse array of products, or demand the use of commercially unavailable starting materials or reagents. In the framework of our studies on heterocyclic systems[12] and in continuation of our previous investigations on the development of environmentally friendly procedures,[13] we recently communicated a procedure for the one-pot chemoselective synthesis of 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives from their corresponding 2-aminophenols by using 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) in the IL [omim][BF_4]. In that work, the IL could be recovered and reused several times without any noticeable loss of performance. Now, report the improved application of the results to the [omim][NO_3]-mediated annulation of 2-aminothiophenols **1** with 2-bromoalkanoates **2** in the presence of no additive, base, or catalyst (Scheme 1). The procedure offers a one-pot mild reaction that takes place at room temperature, incorporates a broad range of starting materials, and provides the possibility of efficiently recycling the IL.

We examined several sets of conditions to optimize the reaction of 2-aminothiophenol **1a** with ethyl 2-bromobutanoate **2c**, as summarized in Table 1. Compared to other carbonate bases, K_2CO_3 showed better performance in several aqueous mixtures of ILs (entries 1–3) to give product **3ac**, although for [omim][NO_3] (entry 4) and [bmim][NO_3] (entry 5) very low conversions were observed. Use of DBU, KF, and Et_3N (entries 6–8) could not lead to better results. In the absence of water, a base, or both, [bmim][BF_4] and [omim][BF_4] were unable to induce significant formation of **3ac** (entries 9–12). To our surprise, both [bmim][NO_3] (entry 13) and [omim][NO_3] (entry 14) showed excellent performance in the absence of water and bases, leading to high formation of **3ac** within 2 h. Conducting the reaction in the absence of any IL gave no product after a long reaction time, proving the effect of the medium in catalyzing the reaction (entry 15). It is noteworthy to mention that under the optimized conditions, 2-aminophenols had very poor participation in similar reactions.



Scheme 1. General pathway for the synthesis of the target products.

Table 1. Optimization of the reaction conditions for the synthesis of **3aa**

Entry	Conditions	Time (h)	Yield %[a]
1	[bmim][BF_4]/H_2O/K_2CO_3	24	98
2	[omim][BF_4]/ H_2O/K_2CO_3	24	88
3	[bmim]Cl/ H_2O/K_2CO_3	24	52
4	[omim][NO_3]/ H_2O/K_2CO_3	24	18
5	[bmim][NO_3]/ H_2O/K_2CO_3	24	7
6	[bmim][BF_4]/ H_2O/DBU	24	48
7	[bmim][BF_4]/ H_2O/KF	24	54
8	[bmim][BF_4]/ H_2O/Et_3N	24	73
9	[bmim][BF_4]/K_2CO_3	24	33
10	[bmim][BF_4]/H_2O	24	0
11	[bmim][BF_4]	24	8
12	[omim][BF_4]	24	22
13	[bmim][NO_3]	2	83
14	[omim][NO_3]	2	96
15	no IL	24	0

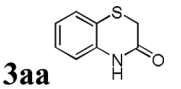
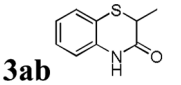
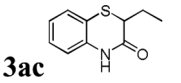
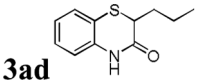
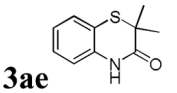
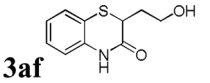
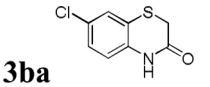
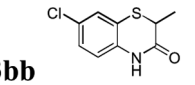
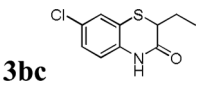
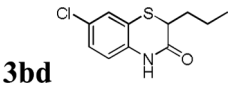
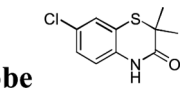
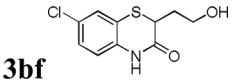
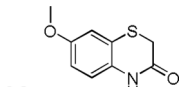
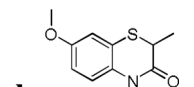
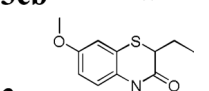
[a]Isolated yields.

Next, the optimized conditions ([omim][NO_3]/rt) were employed to examine the generality of the procedure (Table 2). Reactions of the parent 2-aminothiophenol **1a** with 2-bromoalkanoates **2a**–**2d** all completed in 2 h and gave good yields of products **3aa**–**3ad** (entries 1–4). The same reaction with ethyl 2-bromo-2-methylpropanoate **2e** also gave the respective product **3ae** but over a much longer time period, presumably because of greater steric hindrance of the substrates (entry 5). The conditions were amenable to the same reaction with 2-bromolactone **2f**, giving **3af** in a very short time interval (entry 6). Use of a starting 2-aminothiophenol bearing an electron-withdrawing substituent (**1b**) gave good yields of the desired products (entries 7–12) in a slightly longer time period. This was attributed to relatively poorer electronic nature of the substrate which has lower nucleophilicity. In contrast, the electron-releasing 5-methoxy-substituted **1c** showed greater reactivity and gave its respective products **3ca**–**cf** in much shorter time periods (entries 13–18).

In all cases discussed for the synthesis of 1,4-benzothiazinones **3**, reactions were completed at room temperature in relatively short time periods and products were readily extracted by ether, precipitated by partial removal of the ether content, and purified by recrystallization from Et_2O. This allowed us to save time, solvents, and adsorbents by avoiding chromatography of the crude reaction mixtures. In addition, the IL was recovered and reused in subsequent reactions without significant loss of activity as shown in five consecutive reactions of **1a** with **2a** (Fig. 1, top). Comparison of the ^1H NMR spectra of the IL before the reaction and after recovery/decolorization process showed no significant deterioration in the quality of the IL, as shown in Fig. 1, bottom.

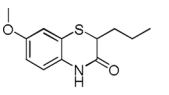
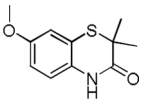
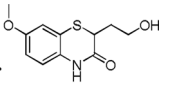
Comparison of the results with previous related methods[7–11] clearly confirms the superiority of the current procedure, where all primary, secondary, and tertiary 2-bromoalkanoates react to give good yields of benzothiazinones in short time periods. A better conclusion can be reached at by the comparison of the results of the present work with those of some other recent procedures, as summarized in Table 3 for products **3aa** and **3ab**.

Table 2. [Omim][NO_3]-catalyzed synthesis of products **3**

Entry	o-Aminothiophenol	2-Bromoalkanoate	Product	Time (h)	Yield %[a]
1	1a	2a	 **3aa**	2	98
2	1a	2b	 **3ab**	2	88
3	1a	2c	 **3ac**	2	92
4	1a	2d	 **3ad**	2	90
5	1a	2e	 **3ae**	20	94
6	1a	2f	 **3af**	1	90
7	1b	2a	 **3ba**	2	92
8	1b	2b	 **3bb**	3	88
9	1b	2c	 **3bc**	3	90
10	1b	2d	 **3bd**	3	88
11	1b	2e	 **3be**	24	90
12	1b	2f	 **3bf**	6	82
13	1c	2a	 **3ca**	0.25	90
14	1c	2b	 **3cb**	0.75	94
15	1c	2c	 **3cc**	0.75	95

(*Continued*)

Table 2. Continued

Entry	o-Aminothiophenol	2-Bromoalkanoate	Product	Time (h)	Yield %[a]
16	1c	2d	 **3cd**	0.75	95
17	1c	2e	 **3ce**	4	80
18	1c	2f	 **3cf**	2	80

[a]Isolated yields.

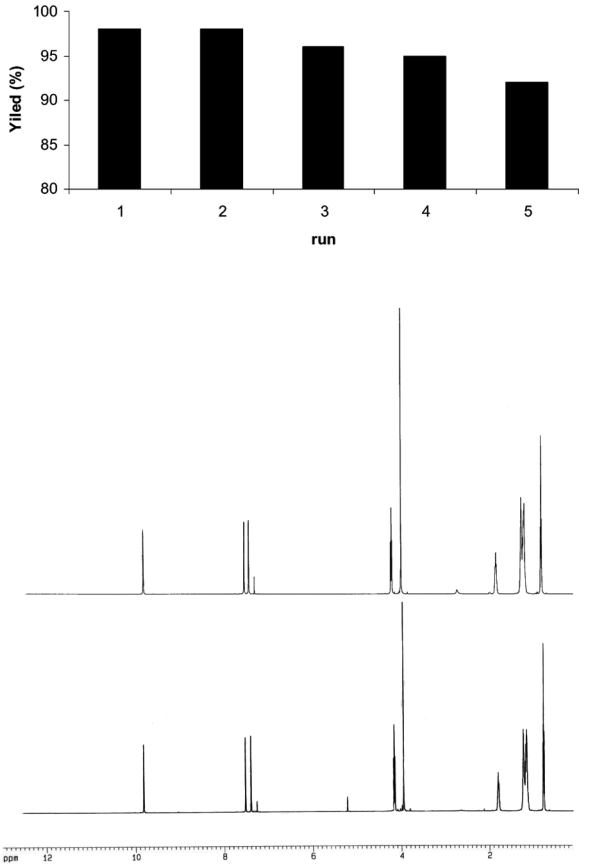


Figure 1. Efficient recovery of the IL (top); ^{1}H NMR spectra of fresh and recovered [omim][NO_3] (bottom).

Table 3. Comparison of the present procedure with some other recent methods

Product	Conditions	Yield (%)	Reference
3aa	[Omim][NO_3], rt, 2 h	98	This work
3aa	KF/alumina/IL, 85 °C, 2.5 h	94	Chhikara et al.[14]
3aa	SmI_2, dry THF, 2 h	83	Zhong et al.[15]
3aa	EtOH, HCl, reflux, 2 steps	60	Cabiddu et al.[16]
3aa	DCM, K_2CO_3, EtOAc, rt to reflux, 14 h, 2 steps	Not given	Borate et al.[17]
3ab	[Omim][NO_3], rt, 2 h	88	This work
3ab	DBU, NMP,[a] MW, 180 °C, 150 psi, 4 min	98	Kamila et al.[18]
3ab	EtOH, EtONa, reflux, 3.5 h	95	Koóš et al.[19]

[a]*N*-Methylpiperidine.

Besides the recovery and reusability of the IL, it is very important from an environmental point of view that the IL in this method is employed without the use of any other additive or base. Indeed, the IL not only dissolves the reactants here but also initiates the reaction by the basicity of its anion and catalyzes the nucleophilic addition of the thiolate to the carbonyl moiety by its coordinative ability. ILs with nitrate ion as their anionic component are known to exhibit strong basicity and coordination abilities and therefore can initiate the reaction by deprotonation of the starting thiophenol.[20] This can justify lack of participation of the less acidic aminophenols when they were subjected to the same reaction conditions.

Based on these, a mechanism can be offered for the procedure where initial deprotonation of the thiol group of the 2-aminothiophenol by the anion of the IL provides the thiophenolate required to attack the electrophilic substrates **2** (or **4**). The ionic liquid as a polar aprotic solvent promotes this process by helping the dissociation of the relatively highly acidic proton of the thiol group. In addition, the affinity of the nitrate ion for hydrogen bonding[21] with thiophenol increases the ease of deprotonation. The reaction is then followed by in situ annulation of the intermediate **A** to give the product (Fig. 2). The mechanism is supported by separation and characterization of the intermediate **A** (where R=R′ = Me, X=Cl). Therefore, it is not surprising that in the presence of water that the efficiency of the

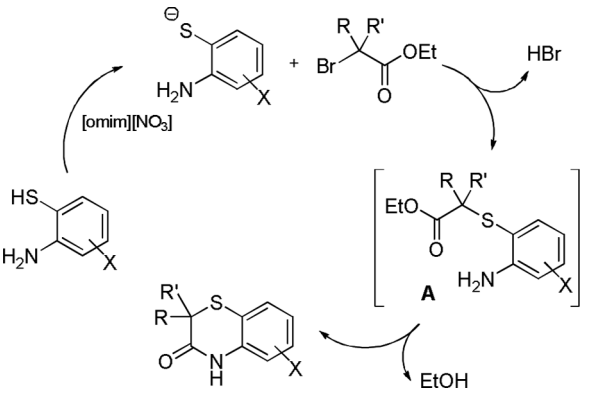


Figure 2. Proposed mechanism.

reaction is diminished (even with K_2CO_3; Table 1, entries 4 and 5) because the basicity of the nitrate ion is lowered due to hydrogen bonding with water molecules.[21]

In summary, the present procedure takes place at room temperature, annulations of 2-aminothiophenols with 2-bromoalkanotes of different steric bulk occur in one pot, reactions are chemoselective, good yields of products are obtained in relatively short time periods, and the IL can be recovered at the end of the process and reused efficiently in the next reactions without any noticeable loss of activity. Moreover no chromatography is required for separation of the products because they could be directly obtained from the crude extracts by concentration of the content. The generality of the reaction and efficient engagement of a variety of the reactants in the procedure make it an interesting and green addition to the present literature archive. Study of the annulation in similar heterocyclic systems is currently under investigation in our laboratory.

EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC) using silica gel–coated plates and EtOAc/hexane solutions as the mobile phase. Melting points are uncorrected. Fourier transform–infrared (FT-IR) spectra were recorded using KBr disks on a Bruker Vector-22 IR spectrometer and absorptions are reported as wave numbers (cm^{-1}). ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained on a FT-NMR Bruker Ultra Shield instrument as $CDCl_3$ solutions and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. ILs were prepared using available procedures.[22] The recovery of the IL was performed by removing its ether content (under reduced pressure at 50 °C for 1 h using a rotary evaporator). Reagents were purchased from commercial sources and were freshly used after being purified by standard procedures. The identity of the known products was confirmed by the comparison of their melting points and their NMR data with those available in the literature.[4b,7b,14,18,23,24] New products were characterized by their ^1H NMR, ^{13}C NMR, IR, and mass spectra, and their purity was confirmed by elemental analyses.

Synthesis of 1-Octyl-3-methylimidazolium Nitrate ([Omim][NO_3])

[Omim][NO_3] was synthesized according to a two-step literature procedure[22d,e] used for the synthesis of [bmim][NO_3] except that 1-bromooctane (19.3 g, 100 mmol) was used instead of 1-bromobutane. The product was obtained as an oil and the overall yield was 84% (21.6 g).

Typical Procedure

A mixture of **1** (1.0 mmol) and **2** (1.0 mmol) in [omim][NO_3] (218 μL, 1 mmol) in a flask was stirred at room temperature for an appropriate length of time. After completion of the reaction, based on TLC monitoring, the reaction mixture was extracted with diethyl ether. The organic phase was washed with brine, dried over anhydrous

Na_2SO_4, and concentrated under reduced pressure to obtain the solid product, which was further purified by recrystallization from ether. The IL was recovered by removing its volatiles under reduced pressure at 80 °C and reused in next reactions without losing its activity.

7-Chloro-2-(2-hydroxyethyl)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3bf)

White solid, mp 132–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (br s, 1H), 7.35 (d, $J = 2.2$ Hz, 1H), 7.18 (dd, $J = 2.2$, 8.5 Hz, 1H), 6.85 (d, $J = 8.5$ Hz, 1H), 3.89–3.81 (m, 2H), 3.73 (t, $J = 7.4$ Hz, 1H), 2.21–2.17 (m, 1H), 1.96 (br s, 1H), 1.95–1.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 135.8, 128.2, 127.7, 127.2, 120.5, 118.4, 58.9, 39.4, 32.8; IR (KBr) cm^{-1} 3404, 3197, 2953, 1662, 1475, 1244, 813, 651; EI-MS (*m*/*z*) 243 [M$^+$] 212, 170, 95. Elemental analyses calcd. for $C_{10}H_{10}ClNO_2S$: C, 49.28%; H, 4.14; N, 5.75; S, 13.16. Found: C, 49.37%; H, 4.18; N, 5.88; S, 13.20.

7-Methoxy-2-methyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3cb)

White solid: mp 126–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (br s, 1H), 6.87 (d, $J = 2.5$ Hz, 1H), 6.86 (d, $J = 8.5$ Hz, 1H), 6.76 (dd, $J = 2.5$, 8.5 Hz, 1H), 3.81 (s, 3H), 3.57 (q, $J = 7.1$ Hz, 1H), 1.52 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 156.3, 130.2, 120.8, 118.5, 113.8, 113.2, 56.1, 37.6, 16.0. IR (KBr) cm^{-1} 3199, 2966, 1664, 1498, 1228, 810, 569; EI-MS (*m*/*z*) 209 [M$^+$], 194, 166, 150. Elemental analyses calcd. for $C_{10}H_{11}NO_2S$: C, 57.39%; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.21%; H, 5.38; N, 6.57; S, 15.33.

2-Ethyl-7-methoxy-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3cc)

White solid, mp 113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (br s, 1H), 6.87 (d, $J = 2.5$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 6.75 (dd, $J = 2.5$, 8.0 Hz, 1H), 3.81 (s, 3H), 3.34 (dd, $J = 6.0$, 8.8 Hz, 1H), 2.02–1.93 (m, 1H), 1.71–1.62 (m, 1H), 1.10 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 156.3, 130.1, 120.1, 118.3, 113.7, 113.4, 56.0, 45.0, 23.7, 11.8; IR (KBr) cm^{-1} 3180, 2954, 1670, 1494, 1232, 869, 621; EI-MS (*m*/*z*) 223 [M$^+$], 194, 166, 150. Elemental analyses calcd. for $C_{11}H_{13}NO_2S$: C, 59.17%; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.53%; H, 5.87; N, 6.20; S, 14.30.

7-Methoxy-2-propyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3 cd)

White solid, mp 115–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (br s, 1H), 6.87 (d, $J = 2.5$ Hz, 1H), 6.86 (d, $J = 8.5$ Hz, 1H), 6.75 (dd, $J = 2.5$, 8.5 Hz, 1H), 3.81 (s, 3H), 3.43 (dd, $J = 2.9$, 6.0 Hz, 1H), 1.92–1.88 (m, 1H), 1.65–1.58 (m, 2H), 1.58–1.47 (m, 1H), 0.95 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 156.3, 130.1, 120.2, 118.3, 113.6, 113.4, 56.0, 43.0, 32.2, 20.3, 13.9; IR (KBr) cm^{-1}) 3170, 3064, 2939, 1664, 1490, 813, 597; EI-MS (*m*/*z*) 237 [M$^+$], 195, 166, 151. Elemental analyses calcd. for $C_{12}H_{15}NO_2S$: C, 60.73%; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.78%; H, 6.44; N, 5.84; S, 13.39.

2-(2-Hydroxyethyl)-7-methoxy-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (3cf)

White solid, mp 138-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (br s, 1H), 6.87 (d, $J = 2.5$ Hz, 1H), 6.86 (d, $J = 8.5$ Hz, 1H), 6.75 (dd, $J = 2.5$, 8.5 Hz, 1H), 3.88–3.82 (m, 2H), 3.80 (s, 3H), 3.70 (t, $J = 7.4$ Hz, 1H), 2.42 (br s, 1H), 2.21–2.14 ((m, 1H), 1.96–1.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 156.5, 129.8, 120.4, 118.5, 113.9, 113.4, 60.1, 56.0, 40.2, 33.1; IR (KBr) cm^{-1} 3412, 3192, 1672, 1494, 1232, 817, 603; EI-MS (m/z) 240 [M$^+$], 209, 167, 124, 56. Elemental analyses calcd. for $C_{11}H_{13}NO_3S$: C, 55.21%; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.27%; H, 5.64; N, 5.62; S, 13.46.

Intermediate A

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, $J = 2.4$ Hz, 1H), 7.15 (dd, $J = 8.6$ Hz, 2.4 Hz, 1H), 6.72 (d, $J = 8.6$ Hz, 1H), 4.16 (s, 1H), 4.13 (q, 2H), 1.55 (s, 6H), 1.24 (t, 3H).

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