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ONE-POT SYNTHESIS OF 2-ARYL- AND 2-ALKYLBENZO-THIAZOLES UNDER MICROWAVE IRRADIATION

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Abstract - Eco-friendly direct solvent-free reactions of o-aminothiophenol and aromatic or aliphatic β-keto esters with microwave irradiation produced 2-substituted benzothiazoles in excellent yield. Experiments that compared microwave irradiation to conventional heating methods showed that the former gives the 2-substituted benzothiazoles faster and in higher yields. The formation of the titled compounds probably involves the nucleophilic addition of the thiol group to the keto group of the β-keto ester with subsequent elimination of ethyl acetate from the resulting adduct. The adduct then undergoes an intramolecular addition of the o-amino group to the carbonyl group to give an adduct from which water is eliminated to afford the 2- substituted benzothiazoles.

INTRODUCTION

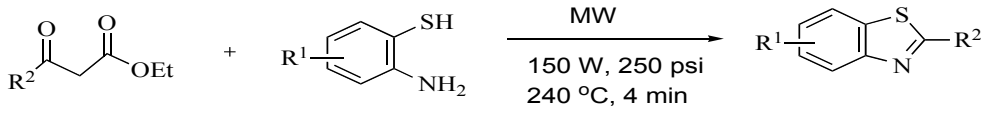
Recently, we have developed synthetic strategies for the preparation of a variety of structurally modified heterocyclic compounds of medicinal interest.[1-4] Here we report on a new method for preparing 2-substituted benzothiazoles. Our interest in these heterocycles comes from several sources. For example, 2-substituted benzothiazoles are active against *Nematospiroideas dubius,*[5] *Ascaris suu* [6] and *Hymemolepis* nana.[7] In addition, benzothiazoles possessing 3-pyridinyl derivatives have greater anthelmintic[7] activities than unsubstituted benzimidazoles.[8a] Also, certain benzothiazoles behave as potential anti-inflammatory agents,[8b] and many 1,3-benzothiazoles have good fluorescent properties.[9]
There are several methods [7,8,10] for preparing arylbenzothiazoles. Most of them involve tedious routes or

require the use of expensive chemicals. The microwave-assisted synthesis[11(a)] offers considerable advantages over conventional heating because of rapid heating and substantial rate enhancements of a wide range of organic reactions. Cleaner reactions are also commonly achieved with marked improvement in yield and in selectivity.[11(b)]

Recently, the use of microwave irradiation for one-step syntheses of 2-substituted benzothiazoles by a two-component system have been reported.[12,13] In those studies, a carboxylic acid or aldehyde and *o*-aminothiophenol were first supported on silica gel, and then subjected to microwave irradiation to give the corresponding 2-substitued benzothiazoles in modest yields (61–81%). We report an improved, more eco-friendly synthesis of 2-substituted benzothiazoles with significantly higher yields (93-99%) by the reaction of aromatic and aliphatic β-keto esters and *o*-aminothiophenols under microwave irradiation without solvent or the use of solid support.

RESULTS AND DISCUSSION

The synthesis of benzothiazoles involves (Scheme1) the microwave (MW) irradiation of a 1:1 equivalent mixture of *o*-aminothiophenol and the appropriate alkyl or aryl β-keto ester. The results are shown in Table 1. Most products obtained were solids and thus were recrystallized from ethyl acetate-hexane mixtures. The liquid products were purified by column chromatography using a 1:4 solution of ethyl acetate-hexane as eluent.



1 **2** **3**

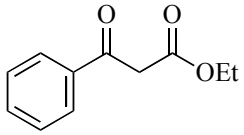
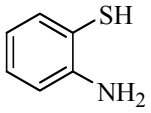
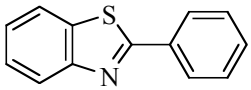
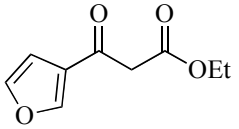
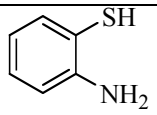
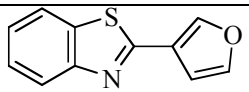
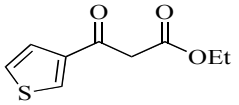
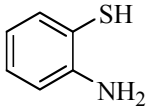
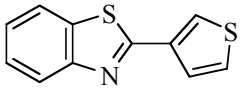
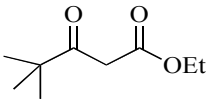
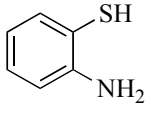
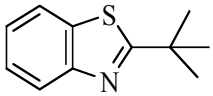
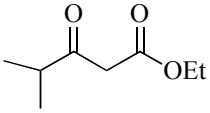
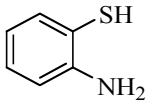
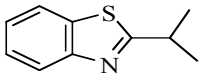
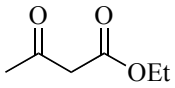
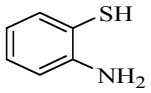
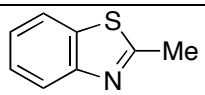
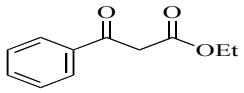
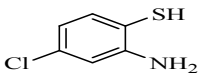
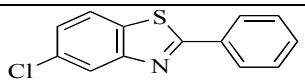
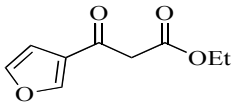
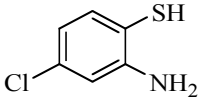
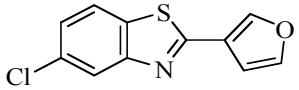
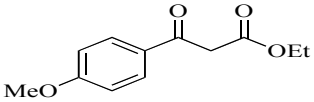
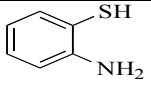
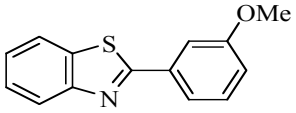
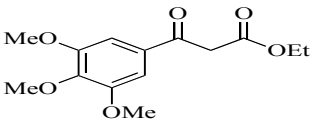
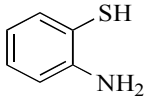
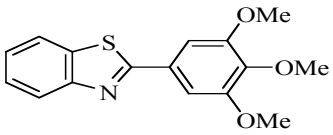
Scheme 1

The structures of **3a-j** were assigned on the basis of ^{1}H NMR and ^{13}C NMR spectroscopy and in case of **3b** by X-Ray crystallographic analysis. An ORTEP drawing of **3b** is shown in Figure 1.

The experimental procedure is quite easy; one mixes the *o*-aminothiophenol and the β-keto ester in a tightly capped test tube that is then subjected to microwave irradiation (150 W output, 250 psi) without solvent or solid support. The reactions were performed either under wattage control or temperature control (240 °C) with no significant differences in reaction times or yields. We also were able to scale up these reactions to give multi-gram quantities of **3** in similar yields. For example 3 g (98% yield) of 2-phenyl benzothiazole (**3a**) was obtained from the reaction of *o*-aminothiophenol (**2a**) and ethyl benzoyl acetate (**1a**) in a one batch reaction.

Marx[14] reported that treatment of *o*-aminothiophenol (**2a**) with the *β*-keto ester (**1f**) in boiling xylene solution for 30 min gave the seven-membered compound, 2-methyl-6,7-benzo-1-thia-5-azacyclohepta-

Table 1 Preparation of Benzothiazoles

Entry	β–Keto ester	Aminothiophenol	Product	Yield, %
1	 **1a**	 **2a**	 **3a**	98
2	 **1b**	 **2a**	 **3b**	97
3	 **1c**	 **2a**	 **3c**	98
4	 **1d**	 **2a**	 **3d**	95
5	 **1e**	 **2a**	 **3e**	93
6	 **1f**	 **2a**	 **3f**	96
7	 **1a**	 **2b**	 **3g**	97
8	 **1b**	 **2b**	 **3h**	96
9	 **1g**	 **2a**	 **3i**	97
10	 **1h**	 **2a**	 **3j**	99

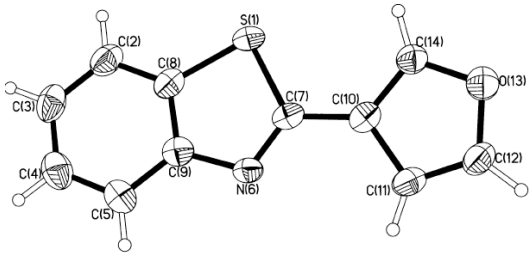
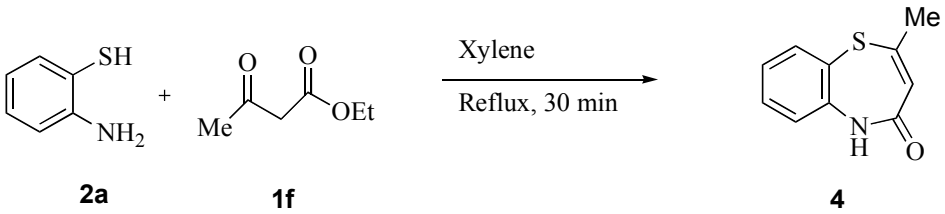


Figure 1 ORTEP structure of compound (**3b**).

benzothiazapine (**4**) was obtained in only 28% yield (see Scheme 2); none of the expected benzothiazoles were observed. However, when we repeated the same reaction in xylene with microwave irradiation, 2-methylbenzothiazole (**3f**), rather than **4**, was obtained, but again in a poor yield of 20%.

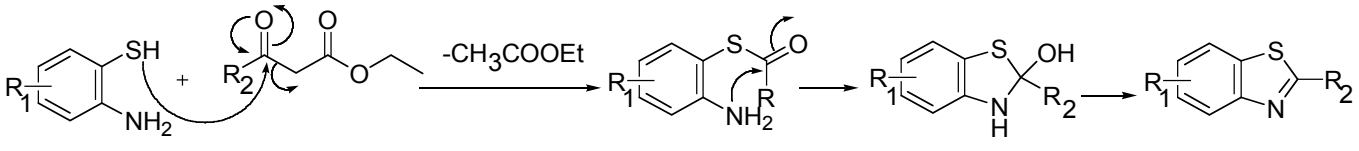


2a **1f** **4**

Scheme 2

Evidence of the microwave effect in this solvent-free reaction, where the possible specific effects are not moderated or impeded by solvents, was obtained by comparing yields of **3a** from the reactions of **1a** and **2a** run for 4 min at various temperatures using microwave irradiation and conventional heating. We started these experiments by running the reactions at room temperature. As these 4-min reactions were subsequently carried out at increasingly higher temperatures, the relative yields of **3a** gradually increased reaching a maximum at 240 °C where the yield of **3a** was ~4 times greater under microwave irradiation (98%) as compared to that (24%) under conventional heating.

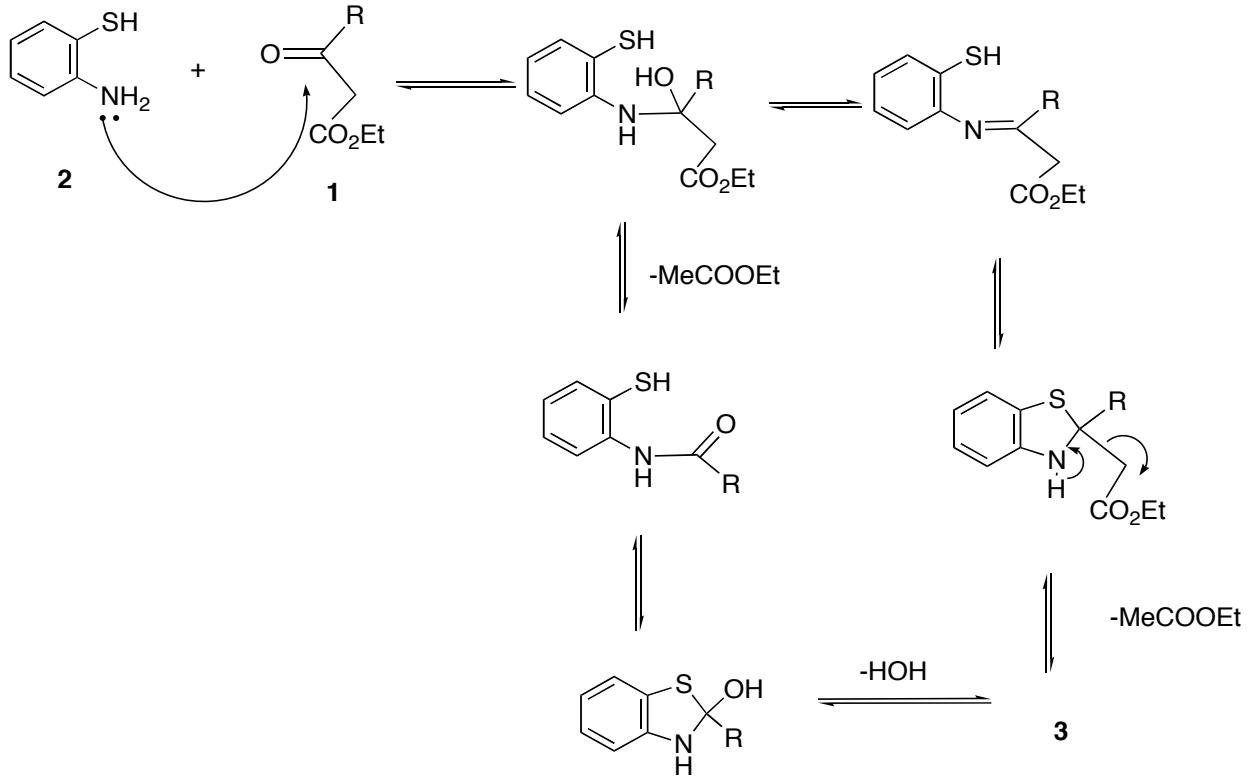
A possible mechanism shown in Scheme 3 involves nucleophilic attack by the sulfur atom of **2** to the carbonyl carbon rather than the ester carbonyl of **1** with the subsequent elimination of ethyl acetate affording adduct (**5**). Ethyl acetate was detected by GC/MS spectral analysis of the reaction mixtures. Adduct (**5**) then undergoes intramolecular nucleophilic addition of the amino group to the carbonyl group to give the 2-hydroxybenzothiazole (**6**). Elimination of water from **6** affords the product (**3**).



2 **1** **5** **6** **3**

Scheme 3 Possible Mechanism for the Synthesis of Benzothiazoles (**3**)

A referee has suggested another possible mechanism which, as shown in Scheme 4, involves the initial addition of the amino group of **2** rather than the thiol group onto the carbonyl group. There is some



Scheme 4

literature precedent for this in that Itoh *et al.*[15] have postulated a similar addition between **2** and an aldehyde. At this time, there is not sufficient data to decide upon the two above mechanism.

CONCLUSIONS

In summary, we have developed a high yield, efficient, solvent free method using microwave irradiation for the synthesis of 2-alkyl- and 2-arylbenzothiazoles. The yields are for the most part significantly lower than those obtained in this investigation. The successful use of microwave irradiation in this study provides yet another example of the participation of specific effects in some microwave-assisted organic syntheses.

EXPERIMENTAL

General Data: Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker ADVANCE DRX-400 Multinuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. The microwave irradiation reactions were carried out in a CEM-Driver instrument at 240 °C and 150 W voltage with 250 PSI pressure. Elemental analyses were obtained from the SMU Analytical

Service Laboratories. All chemicals were purchased from Aldrich Chemicals.

General procedure: The appropriate *o*-aminothiophenol (1.6 mmol) and aromatic or aliphatic β-keto ester (1.6 mmol) were mixed and the resulting mixture was heated under MW irradiation condition at 240 °C for 4 min. The resulting solid mixtures were recrystallized from ethyl acetate-hexane to obtain the titled compounds. The liquid product mixtures were purified by column chromatography using ethyl acetate-hexane (1:4) as eluent. The results are shown below.

2-Phenylbenzothiazole (3a): Isolated as a white crystalline solid (ethyl acetate-hexane), mp 112–114 °C. ^{1}H NMR ($CDCl_3$) δ 7.41 (dd, *J* = 2.5, 8.0 Hz, 1H, aromatic), 7.50–7.52 (m, 4H, aromatic), 7.93 (dd, *J* = 2.5, 7.8 Hz, 1H, aromatic), 8.09–8.10 (m, 3H, aromatic). ^{13}C NMR ($CDCl_3$) δ 122.0, 123.6, 125.6, 126.7, 127.9, 129.4, 131.3, 134.0, 135.5, 154.5, 168.5. *Anal*. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63. Found: C, 73.99; H, 4.38; N, 6.70.

2-(Furan-3-yl)benzothiazole (3b): Isolated as a yellow solid (CH_2Cl_2-hexane), mp 83–84 °C. ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1H, aromatic), 7.39 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.50 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.55 (s, 1H, aromatic), 7.88 (d, *J* = 8.0 Hz, 1H, aromatic), 8.04 (d, *J* = 8.0 Hz, 1H, aromatic), 8.13 (s, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 109.6, 121.9, 122.2, 123.2, 125.5, 126.7, 134.7, 143.0, 144.6, 154.1, 160.0. *Anal*. Calcd for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.43; H, 3.50; N, 7.01.

2-(3-Thienyl)benzothiazole (3c): Isolated as a yellow solid, mp 91–93°C (pentane). ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 1H, aromatic), 7.29 (s, 1H, aromatic), 7.40 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.49 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.55 (s, 1H, aromatic), 7.79 (d, *J* = 7.8 Hz, 1H, aromatic), 8.10 (d, *J* = 7.8 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 121.9, 122.0, 123.0, 124.9, 125.1, 126.1, 127.3, 133.3, 141.9, 154.3, 166.1. *Anal*. Calcd for $C_{11}H_7NS_2$: C, 60.80; H, 3.25; N, 6.45. Found: C, 60.84; H, 3.30; N, 6.44.

2-*tert*-Butylbenzothiazole (3d): Isolated as a yellow solid mp 65–68 °C (ethyl acetate-hexane). ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H, *t*-Bu), 7.46 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.74 (d, *J* = 7.8 Hz, 1H, aromatic), 7.87 (d, *J* = 7.8 Hz, 1H, aromatic), 8.00 (d, *J* = 7.8 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 31.3 (x3), 39.1, 122.3, 122.5, 125.1, 125.3, 133.4, 154.5, 167.1. *Anal*. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.15; H, 6.88; N, 7.39.

2-Isopropylbenzothiazole (3e): Isolated as a brown viscous liquid. ^{1}H NMR ($CDCl_3$) δ 1.51 (d, *J* = 4.0 Hz, 6H, ($C\underline{H}_3)_2CH$-), 3.41–3.45 [m, 1H, -$C\underline{H}(CH_3)_2$], 7.36 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.47 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.87 (d, *J* = 7.8 Hz, 1H, aromatic), 8.01 (d, *J* = 7.8 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 23.9 (x2), 39.1, 121.9, 122.1, 125.3, 125.8, 133.5, 153.1, 166.3. *Anal*. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.90. Found: C, 67.87; H, 6.33; N, 7.99.

2-Methylbenzothiazole (3f): Isolated as a viscous oil. ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 3H, CH_3), 7.31 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.42 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.79 (d, *J* = 7.8 Hz, 1H, aromatic),

7.95 (d, *J* = 8.0 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 20.4, 121.7, 122.7, 125.0, 126.2, 136.0, 153.7, 167.2. *Anal*. Calcd for C_8H_7NS: C, 64.39; H, 4.73; N, 9.39. Found: C, 64.50; H, 4.80; N, 9.30.

5-Chloro-2-phenylbenzothiazole (3g): Isolated as a yellow solid mp 102–105 °C (CH_2Cl_2-hexane). ^{1}H NMR ($CDCl_3$) δ 7.38 (dd, *J* = 7.8, 8.0 Hz, 2H, aromatic), 7.49–7.53 (m, 4H, aromatic), 7.83 (dd, *J* = 2.5, 7.8 Hz, 1H, aromatic), 8.10 (d, *J* = 7.8 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.9, 124.5, 126.3, 127.0, 128.5, 129.3, 129.5, 130.1, 133.1, 136.9, 154.5, 169.5. *Anal*. Calcd for $C_{13}H_8NClS$: C, 63.54; H, 3.28; N, 5.70. Found: C, 63.58; H, 3.37; N, 5.78.

5-Chloro-2-(furan-3-yl)benzothiazole (3h): Isolated as a white solid, mp 89–92 °C (CH_2Cl_2-hexane), ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 1H, aromatic), 7.40 (s, 1H, aromatic), 7.51 (d, *J* =7.8 Hz, 1H, aromatic), 7.88 (d, *J* =2.5 Hz, 1H, aromatic), 8.05 (d, *J* = 7.8 Hz, 1H, aromatic), 8.13 (s, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 109.5, 121.3, 122.3, 123.2, 125.5, 126.8, 134.7, 143.5, 144.6, 154.1, 162.1. *Anal*. Calcd for $C_{11}H_6NClS$: C, 56.06; H, 2.57; N, 5.94. Found: C, 56.20; H, 2.68; N, 5.97.

2-(3'-Methoxyphenyl)benzothiazole (3i): Isolated as a yellow viscous liquid. ^{1}H NMR ($CDCl_3$) δ 3.93(s, 3H, OMe), 7.05(dd, *J* = 1.8, 8.0 Hz, 1H, aromatic), 7.41 (dd, *J* = 4.0, 8.0 Hz, 2H, aromatic), 7.51(dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.66 (d, *J* = 8.0 Hz, 1H, aromatic), 7.70 (s, 1H, aromatic), 7.91 (d, *J* = 8.0 Hz, 1H, aromatic), 8.10 (d, *J* = 8.0 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 55.91, 112.4, 117.7, 120.6, 122.0, 123.6, 125.6, 126.7, 130.4, 135.2, 135.4, 154.4, 160.4, 168.4. *Anal*. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.81; H, 4.66; N, 5.85.

2-(3',4',5'-Trimethoxyphenyl)benzothiazole (3j): Isolated as a yellow solid mp 95–98 °C (ethyl acetate-hexane).^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OMe), 3.98 (s, 3H, -OMe), 3.99 (s, 3H, OMe), 7.2 (s, 1H, aromatic), 7.33–7.40 (m, 2H, aromatic), 7.48 (dd, *J* =7.8, 8.0 Hz, 1H, aromatic), 7.89 (dd, *J* = 2.5, 7.8 Hz, 1H, aromatic), 8.07 (dd, *J* = 2.5, 7.8 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 56.69, 56.76, 61.3, 105.2, 106.2, 121.9, 123.4, 125.5, 126.7, 129.4, 135.4, 141.0, 153.4, 153.9, 154.4, 168.2. *Anal*. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.80; H, 5.11; N, 4.70.

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