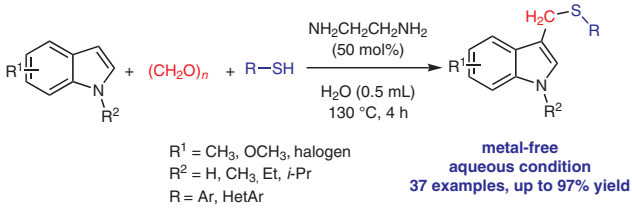
Synlett F. Xiao et al. Letter

Base-Promoted Three-Component One-Pot Synthesis of 3- (Thiomethyl)indoles with Paraformaldehyde under Aqueous Conditions

Fuhong Xiao*
Shanshan Yuan
Huawen Huang
Guo-Jun Deng*

Key Laboratory for Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, P. R. of China
fhxiao@xtu.edu.cn
gjdeng@xtu.edu.cn



Received: 09:08:2018
Accepted after revision: 24:09:2018
Published online: 17.10.2018
DOI: 10.1055/s-0037-1611023; Art ID: st-2018-u0507-l

Abstract An ethylenediamine-promoted three-component synthesis of 3-(thiomethyl)indoles from indoles, thiophenols, and paraformaldehyde has been developed. Water is used as the green solvent in a simple and environmentally friendly procedure. Stable and low-toxicity paraformaldehyde is used as a carbon source.

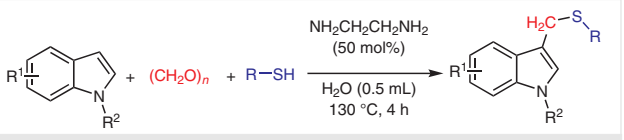
Key words metal-free, aqueous conditions, paraformaldehyde, multicomponent reaction, thiomethylation, thiomethylindoles

Indole and its derivatives are widely present in a variety of naturally occurring products, and they are extremely important in medicinal chemistry for their biological activities.[1] In particular, 3-substituted indoles have played major roles in the preparation of privileged medicinal scaffolds that exhibit a wide range of biological activities, such as antioxidant, antibacterial, antiinsecticidal, and anticancer activities as well as antibiotic central-nervous-system modulation.[2] Consequently, numerous methods for the synthesis of these compounds have been developed.[3] However, very few methods have been developed for the synthesis of 3-thiomethyl-substituted indoles.

Two general methods for the synthesis of 3-[(alkyl/aryl)thio(aryl)methyl]indole derivatives are (1) the Lewis acid-catalyzed three-component reaction of indoles, aldehydes, and thiols,[4] and (2) the Lewis acid-catalyzed S_N1-type reaction of indol-3-ylmethanols with thiols.[5] Despite the merits of these methods, they suffer from some limitations such as the need for prior functionalization of the indolyl alcohol or the use of metal catalysts and organic solvents. It is therefore desirable to develop new methods for the synthesis of 3-thiomethyl-substituted indoles under green conditions.

Paraformaldehyde has been receiving more and more attention because of its advantages in terms of low cost, stability, and low toxicity.[6] Moreover, it has been used as a one-carbon homologation reagent for the synthesis of an incredible variety of complicated skeletons.[7] In recent years, various methods have been developed that use paraformaldehyde to install methylene,[8] carbonyl,[9] or hydroxymethyl groups[10] into various substrates. With respect to our recent studies on paraformaldehyde insertion to construct heterocycles, we have reported new methods for synthesizing phthalazinones,[11] 2-aroylbenzofurans,[12] and quinazolines[13] by using paraformaldehyde as a carbon source.

From the perspective of green chemistry, water is a desirable reaction medium because of its low cost, low toxicity, and environmental friendliness. Inspired by previous works, as well as by our recent success in using water as an ideal solvent for the C–H sulfenylation,[14] we have developed a new and efficient approach to the synthesis of 3-(thiomethyl)indoles through C–H bond functionalization of indoles with arylthiols and paraformaldehyde under aqueous conditions (Scheme 1). This method offers new access to various substituted 3-(thiomethyl)indoles in good yields by using paraformaldehyde as a carbon source. The mild and transition-metal-free reaction conditions are attractive features of this method.

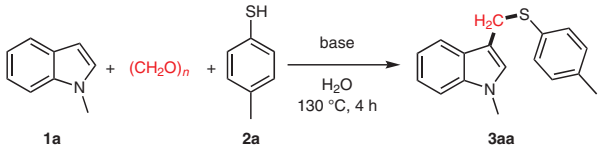


Scheme 1 New strategy for the synthesis of 3-(thiomethyl)indoles.

We begin our research by investigating the reaction of 1-methylindole (**1a**) with 4-methylbenzenethiol (**2a**) in water at 130 °C with K_2CO_3 as a base, and we obtained the

desired product **3aa** in 47% yield, as determined by GC and NMR analysis (Table 1, entry 1). Then, a variety of bases were investigated (entries 2–11), among which ethylenediamine was the most efficient, giving product **3aa** in 84% yield (entry 11). Slightly lower yields were obtained when the reaction was run at 110 °C (entry 12). It was necessary to use 50 mol% of ethylenediamine to obtain a satisfactory yield, as the yield decreased to 49% when 20 mol% of the base was used (entry 13). As a control experiment showed, none of the desired product **3aa** was obtained in the absence of paraformaldehyde (entry 14). A base is necessary for the reaction to proceed, as the product was obtained in only 20% yield in the absence of a base (entry 15).

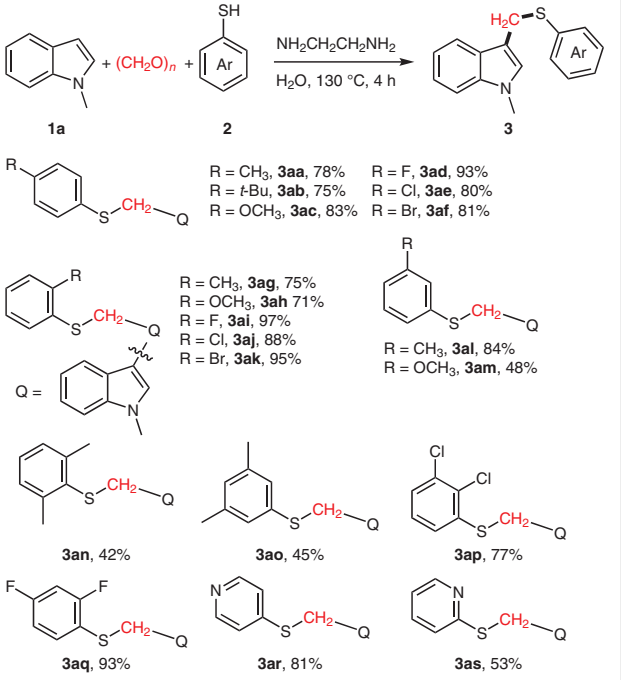
Table 1 Optimization of the Reaction Conditions[a]



Entry	Base	Yield[b] (%)
1	K_2CO_3	47
2	Li_2CO_3	39
3	Cs_2CO_3	58
4	KOH	53
5	NaOEt	44
6	piperidine	50
7	Et_3N	61
8	pyridine	50
9	$PhNH_2$	36
10	Bu_2NH	22
11	$H_2N(CH_2)_2NH_2$	84
12[c]	$H_2N(CH_2)_2NH_2$	79
13[d]	$H_2N(CH_2)_2NH_2$	49
14[e]	$H_2N(CH_2)_2NH_2$	0
15	–	20

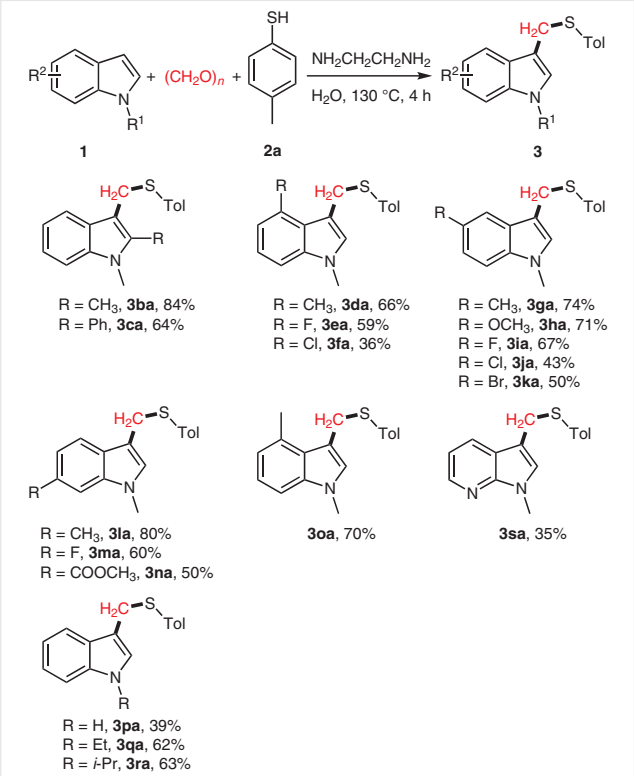
[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), base (50 mol%), paraformaldehyde (0.8 mmol), H_2O (0.5 mL), 130 °C, 4 h, air.
[b] GC yield.
[c] At 110 °C.
[d] $H_2N(CH_2)_2NH_2$ (20 mol%).
[e] Without paraformaldehyde.

With the optimized reaction conditions in hand, we investigated the substrate scope with respect to the thiophenol (Scheme 2). The model reaction of 1-methylindole (**1a**) with 4-methylbenzenethiol (**2a**) gave the desired product **3aa** in 78% isolated yield. Other *para*-substituted thiophenols reacted smoothly with **1a** to give the corresponding products **3ab–af** in high yields. The position of the substituent on the benzene ring (*ortho* or *meta*) did not affect the reaction yield significantly (**3ag–3ai**), except in the case of 3-methoxybenzenethiol (**2m**). Modest yields were obtained when 2,6-dimethylbenzenethiol (**2n**) or 3,5-dimethylbenzenethiol (**2o**) was used as the substrate. When 2,3-dichlorobenzenethiol (**2p**) or 2,4-difluorobenzenethiol (**2q**) was employed, the corresponding products **3ap** and **3aq** were obtained in 77% and 93% yield, respectively. To our delight, heteroaromatic thiols such as **2r** and **2s** also participated in the reaction to provide the corresponding product **3ar** and **3as** in moderate to good yield. Unfortunately, aliphatic thiols were less effective coupling partners under the current reaction conditions.



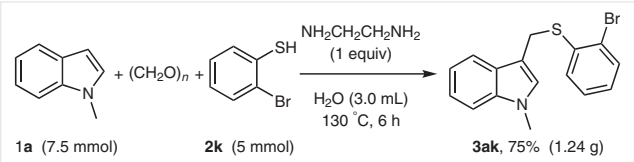
Scheme 2 Reaction of indole with thiophenols. *Reaction conditions*: **1a** (0.4 mmol), **2** (0.2 mmol), ethylenediamine (50 mol%), paraformaldehyde (0.8 mmol), H_2O (0.5 mL), 130 °C, 4 h, air. Isolated yields are reported.

The influence of substituents on the indole moiety was also evaluated (Scheme 3). Indoles bearing various substituents coupled smoothly with 4-methylbenzenethiol (**2a**). Promising yields were obtained when a methyl group was present in the C-2, C-4, C-5, or C-6 position of the indole ring. However, the yield decreased dramatically when 4-, 5-, or 6-haloindole was used as a substrate. The product **3na** was obtained in 50% yield, showing that an ester group is tolerated. Protected 1-ethyl-1*H*-indole (**1q**) and 1-isopropyl-1*H*-indole (**1r**) could also be employed in this reaction and they gave the desired products **3qa** and **3ra** in the 62% and 63% yield, respectively. Unfortunately, the yield decreased markedly when 1*H*-indole (**1p**) was used as a substrate. 1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**1s**) also coupled with 4-methylbenzenethiol (**2a**) to give the desired product **3sa** in 35% yield.



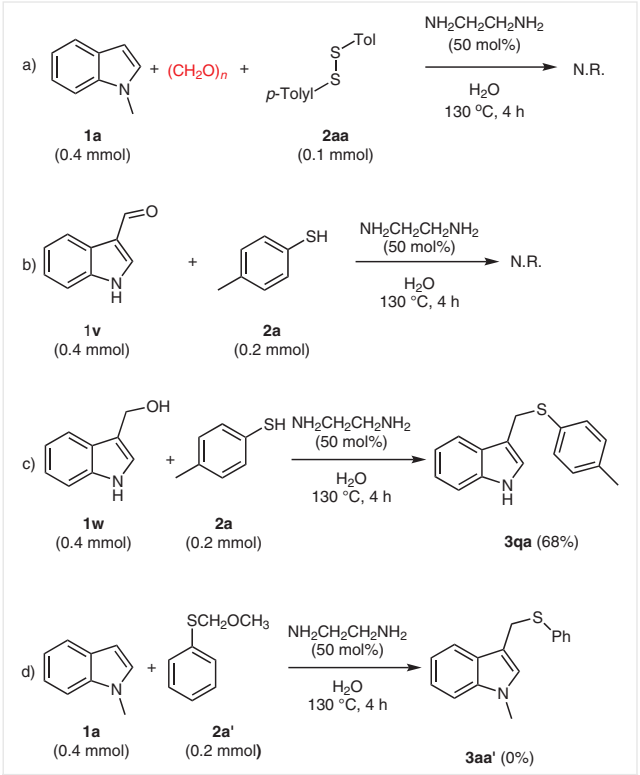
Scheme 3 Substrate scope with respect to the indole. *Reaction conditions*: **1** (0.4 mmol), **2a** (0.2 mmol), ethylenediamine (50 mol%), paraformaldehyde (0.8 mmol), H_2O (0.5 mL), 130 °C, 4 h, air. Isolated yields are reported.

To demonstrate the synthetic utility of the new method, we then carried out a gram-scale reaction (Scheme 4). Intriguingly the reaction of 1-methyl-1*H*-indole (**1a**, 7.5 mmol) with 2-bromobenzenethiol (**2k**) in 3 mL of H_2O afforded the corresponding aryl sulfide **3ak** in 75% yield. This showed that that our protocol can be used as a practical method to synthesize precursors of some bioactive molecules.[15]



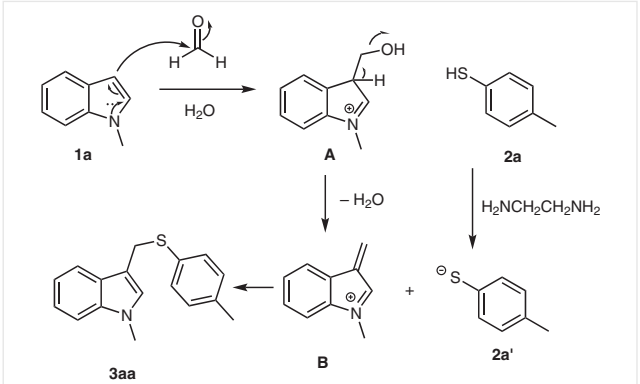
Scheme 4 Gram-scale reaction

To gather mechanistic information, we set up some control experiments under various reaction conditions. No reaction occurred upon treatment of 1-methylindole (**1a**) with bis(4-tolyl) disulfide (**2aa**) and paraformaldehyde under the optimized reaction conditions [Scheme 5(a)]. None of the desired product was obtained when 1*H*-indole-3-carbaldehyde (**1v**) was treated with 4-methylbenzenethiol [Scheme 3(b)]. Coupling of (1*H*-indol-3-yl)methanol (**1w**) with 4-methylbenzenethiol afforded the desired product **3qa** in 68% yield [Scheme 5(c)]. Moreover, none of the desired product was obtained when [(methoxymethyl)thio]benzene (**2a'**) was used as substrate [Scheme 5(d)].



Scheme 5 Control experiments under various conditions

On the basis of these control experiments and related reports in the literature,[4a,4b] we propose the possible mechanism shown in Scheme 6. Initially, formaldehyde is attacked by the 1-methylindole nucleophile to form the iminium ion **A**; this, in turn, eliminates one molecule of



Scheme 6 Proposed mechanism

water to form intermediate **B** through an E2 or E1cb elimination pathway. Intermediate **B** then reacts with the thiophenol anion **2a′**, generated from **2a** by base-mediated deprotonation, to afford the final product **3aa**.

In conclusion, we have developed a metal-free, green, and environmentally friendly method for the synthesis of 3-(thiomethyl)indoles under aqueous conditions.[16] Paraformaldehyde, which is stable and has low toxicity, was used as an atom-economic one-carbon source. Various thiophenols used as the sulfur sources coupled smoothly with various indoles. Ethylenediamine was used as a highly effective base for this transformation. Functional groups such as halogens and heterocycles were well tolerated under the optimized reaction conditions. This novel method provides an alternative environmentally friendly and easily handled approach to 3-(thiomethyl)indoles.

Funding Information

We gratefully acknowledge the support for this work provided by the National Natural Science Foundation of China (21572194, 21502160). The project was supported by the Scientific Research Fund of Hunan Provincial Education Department (YB2016B024), the China Postdoctoral Science Foundation Funded Project (2015M572257), and Hunan Provincial Natural Science Foundation of China (16JJ3112).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611023.

References and Notes

(1) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: London, **1970**. (b) *Indoles, Part Four: The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley-Interscience: Hoboken, **1983**. (c) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. (d) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155.

(2) For selected recent examples, see: (a) Mizoguchi, H.; Oguri, H.; Tsuge, K.; Oikawa, H. *Org. Lett.* **2009**, *11*, 3016. (b) Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 7600. (c) Jiang, B.; Yang, C.-G.; Wang, J. *J. Org. Chem.* **2001**, *66*, 4865. (d) Safe, S.; Papineni, S.; Chintharlapalli, S. *Cancer Lett.* **2008**, *269*, 326. (e) Lee, S.-O.; Abdelrahim, M.; Yoon, K.; Chintharlapalli, S.; Papineni, S.; Kim, K.; Wang, H.; Safe, S. *Cancer Res.* **2010**, *70*, 6824. (f) Queiroz, M. M. F.; Queiroz, E. F.; Zeraik, M. L.; Ebrahimi, S. N.; Marcourt, L.; Cuendet, M. I.; Castro-Gamboa, I.; Hamburger, M.; da Silva Bolzani, V.; Wolfender, J.-L. *J. Nat. Prod.* **2014**, *77*, 650.

(3) For selected recent examples, see: (a) Kagawa, N.; Malerich, J. P.; Rawai, V. H. *Org. Lett.* **2008**, *10*, 2381. (b) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8707.

(4) (a) Khorshidi, A.; Shariati, S. *RSC Adv.* **2014**, *4*, 41469. (b) Dar, A. A.; Ali, S.; Khan, A. T. *Tetrahedron Lett.* **2014**, *55*, 486. (c) Parnes, R.; Pappo, D. *Org. Lett.* **2015**, *17*, 2924. (d) Coker, J. N. *J. Org. Chem.* **1962**, *27*, 1881.

(5) (a) Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780. (b) Suárez, A.; Martínez, F.; Sanz, R. *Org. Biomol. Chem.* **2016**, *14*, 11212. (c) Wen, H.; Wang, L.; Xu, L.; Hao, Z.; Shao, C.-L.; Wang, C.-Y.; Xiao, J. *Adv. Synth. Catal.* **2015**, *357*, 4023. (d) Xiao, J.; Wen, H.; Wang, L.; Xu, L.; Hao, Z.; Shao, C.-L.; Wang, C.-Y. *Green Chem.* **2016**, *18*, 1032.

(6) For a review, see: Li, W.; Wu, X.-F. *Adv. Synth. Catal.* **2015**, *357*, 3393.

(7) Taylor, R. T.; O'Sullivan, T. J. In *e-EROS: Encyclopedia of Reagents for Organic Synthesis*; Wiley-Interscience: Chichester, **2008**, ; DOI: 10.1002/047084289X.rp018.pub2.

(8) (a) Li, M.; He, C.; Chen, F.; Gu, Y. *Adv. Synth. Catal.* **2010**, *352*, 519. (b) Park, K.; Heo, Y.; Lee, S. *Org. Lett.* **2013**, *15*, 3322. (c) Ohta, Y.; Kubota, Y.; Watabe, T.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 6299. (d) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 7052. (e) Natte, K.; Li, W.; Zhou, S.; Neumann, H.; Wu, X.-F. *Tetrahedron Lett.* **2015**, *56*, 1118. (f) Man, N. Y. T.; Li, W.; Stewart, S. G.; Wu, X.-F. *Chimia* **2015**, *69*, 345.

(9) (a) Garcia, J. M.; Jones, G. O.; Virwani, K. *Science* **2014**, *344*, 732. (b) Natte, K.; Dumrath, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 10090. (c) Li, W.; Wu, X.-F. *J. Org. Chem.* **2014**, *79*, 10410.

(10) (a) Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705. (b) Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* **2002**, *4*, 1667. (c) Köpfer, K.; Sam, B.; Breit, B.; Krische, M. J. *Chem. Sci.* **2013**, *4*, 1876. (d) Li, W.; Wu, X.-F. *Eur. J. Org. Chem.* **2015**, 331.

(11) Wang, H.; Cai, J.; Huang, H.; Deng, G.-J. *Org. Lett.* **2014**, *16*, 5324.

(12) Cheng, X. F.; Peng, Y.; Wu, J.; Deng, G.-J. *Org. Biomol. Chem.* **2016**, *14*, 2819.

(13) Cheng, X.; Wang, H.; Xiao, F.; Deng, G.-J. *Green Chem.* **2016**, *18*, 5773.

(14) (a) Xiao, F.; Chen, S.; Tian, J.; Huang, H.; Liu, Y.; Deng, G.-J. *Green Chem.* **2016**, *18*, 1538. (b) Xiao, F.; Chen, S.; Li, C.; Huang, H.; Deng, G.-J. *Adv. Synth. Catal.* **2016**, *358*, 3881. (c) Xiao, F.; Tian, J.; Xing, Q.; Huang, H.; Deng, G.-J.; Liu, Y. *ChemistrySelect* **2017**, *2*, 428.

(15) (a) Zhang, X.; Li, X.; Allan, G. F.; Musto, A.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3233. (b) Kang, N.; Lee, J.-M.; Jeon, A.; Oh, H. B.; Moon, B. *Tetrahedron* **2016**, *72*, 5612.

(16) **1-Methyl-3-{[(4-tolyl)thio]methyl}-1*H*-indole (3aa); Typical Procedure**

A 10 mL oven-dried reaction vessel was charged with 1-methyl-1*H*-indole (**1a**, 50 µL, 0.4 mmol), paraformaldehyde (24 mg, 0.8 mmol), 4-methylbenzenethiol (**2a**, 24.8 mg, 0.2 mmol). The vessel was sealed, and ethane-1,2-diamine (6.5 µL, 0.1 mmol) and H_2O (0.5 mL) were added from a syringe. The resulting solution was stirred at 130 °C for 4 h. The volatiles were removed under vacuum, and the residue was purified by column chromatography [silica gel, PE–EtOAc (100:1)] to give a brown liquid; yield: 41.7 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.9 Hz, 1 H), 7.28–7.20 (m, 4 H), 7.14–7.10 (m, 1 H), 7.08–7.06 (m, 2 H), 6.91 (s, 1 H), 4.30 (s, 2 H), 3.69 (s, 3 H), 2.30 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.0, 136.0, 133.6, 130.0, 129.5, 127.7, 127.2, 121.8, 119.2, 119.1, 110.2, 109.3, 32.66, 30.34, 21.00. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}NS$: 268.11545; found: 268.11554.