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Efficient Copper-Catalyzed Synthesis of Substituted Pyrazoles at Room Temperature

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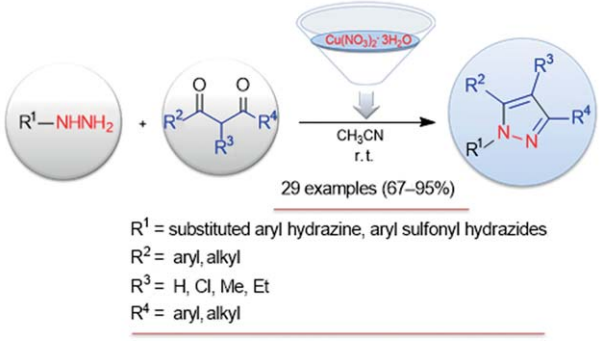

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Abstract An efficient method for the synthesis of pyrazoles through a copper-catalyzed condensation reaction has been developed. The new catalytic system not only maintained a broad substrate scope but was also active under acid-free reaction conditions, overcoming the conventional requirement for an acid-catalyzed system. Furthermore, the copper catalyst enabled this reaction to be performed at room temperature and in a short reaction time.

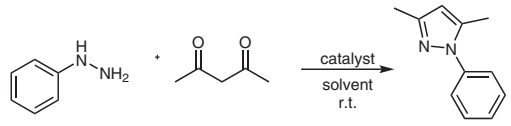
Key words pyrazoles, condensation reaction, copper catalysis, arylhydrazines, sulfonyl hydrazides

Pyrazole and its derivatives represent an important class of fused nitrogen-containing heterocycles. They display a wide spectrum of biological activities and they have long attracted extensive pharmacological, chemical, and synthetic interest.[1] For instance, structural cores containing pyrazole rings offer valuable building blocks for the synthesis of biologically active compounds and are found in many biologically active molecules, such as pharmaceuticals.[2] Consequently, considerable attention has been given to the development of an efficient approach for the construction of substituted pyrazole derivatives, including the condensation of 1,3-dicarbonyl compounds with substituted hydrazines,[3] 1,3-dipolar cycloaddition employing alkenes or alkynes,[4] the reaction of unsaturated aldehydes or ketones with hydrazines,[5] metal-catalyzed oxidative carbonylations of arylhydrazines and alkynes,[6] or functionalizations of unsubstituted pyrazoles,[7] among others.[8] Among the many advantages of these reported methods, the condensation reaction between 1,3-dicarbonyl compounds and substituted hydrazines provides one of the most-efficient and simplest routes for the construction of pyrazoles.

Despite remarkable advances in the last few decades, this method has the following limitations in terms of its practical applications.[9] First, substituted pyrazoles are only accessible in the presence of strongly acidic conditions, for example in the presence of corrosive and environmentally unfriendly hydrochloric or sulfuric acid. Secondly, the conventional process is often performed under harsh conditions by heating at elevated temperature for long reaction times. Thirdly, complex and expensive transition-metal catalysts are used. Therefore, the development of an efficient and convenient method for the synthesis of pyrazole and its derivatives is of great significance and is highly desirable. Copper salts, especially copper nitrate, are abundant in nature and have a vast range of practical uses. Here, we describe an unprecedented process employing low-cost copper nitrate as an acid-free catalyst to afford pyrazole and its derivatives in good yields at room temperature in short reaction times.

First, we determined the optimal conditions for the condensation reaction between phenylhydrazine (**1a**) and pentane-2,4-dione (**2**) in the presence of various copper salts as a model reaction (Table 1). No reaction occurred when copper (II) tartrate hydrate was used as a catalyst in acetonitrile at room temperature (Table 1, entry 1). However, various levels of reactivity were observed when other copper salts were used, and the reaction proceeded smoothly to furnish the pyrazole **3a** (entries 2–6). Importantly, the use of $Cu(NO_3)_2{\cdot}3H_2O$ resulted in a significant increase in yield to 87% (entry 7). Without the addition of any catalyst, none of the desired product was observed (entry 8). We also investigated the effects of various other solvents: ethanol, 1,4-dioxane, dichloromethane, dimethyl sulfoxide, and tetrahydrofuran. Compared with the favorable results obtained with acetonitrile (87% yield; entry 7), ethanol was similarly effective, giving **3a** in 79% yield (entry 9). Tetrahydrofuran and dimethyl sulfoxide were less effective, yielding **3a** in

Table 1 Optimization of the Reaction Conditions.



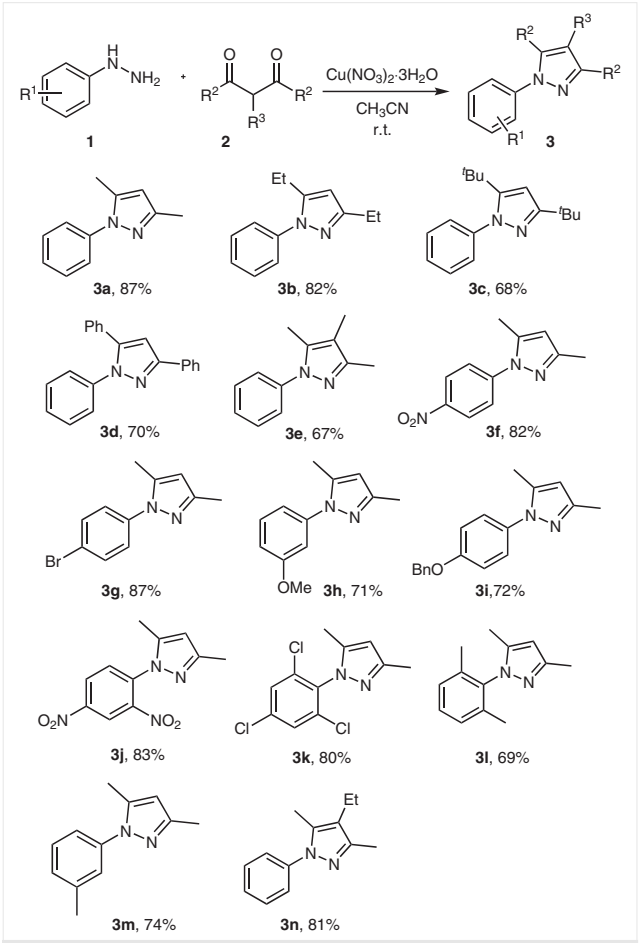
1a 2a 3a

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	Copper(II) tartrate hydrate	CH_3CN	8	trace
2	$CuSO_4$	CH_3CN	1	39
3	$CuCl_2$	CH_3CN	2	36
4	CuCl	CH_3CN	1	64
5	$Cu(OAc)_2$	CH_3CN	1	80
6	CuI	CH_3CN	1	70
7	$Cu(NO_3)_2{\cdot}3H_2O$	CH_3CN	1	87
8	–	CH_3CN	1	0
9	$Cu(NO_3)_2{\cdot}3H_2O$	EtOH	1	79
10	$Cu(NO_3)_2{\cdot}3H_2O$	1,4-dioxane	1	68
11	$Cu(NO_3)_2{\cdot}3H_2O$	CH_2Cl_2	1	66
12	$Cu(NO_3)_2{\cdot}3H_2O$	THF	1	23
13	$Cu(NO_3)_2{\cdot}3H_2O$	DMSO	1	20
14[c]	$Cu(NO_3)_2{\cdot}3H_2O$	CH_3CN	2	55
15[d]	$Cu(NO_3)_2{\cdot}3H_2O$	CH_3CN	1	80

[a] Unless otherwise noted, all reactions were performed with phenylhydrazine (**1a**; 0.5 mmol), catalyst (0.05 mmol) and pentane-2,4-dione (**2a**; 0.6 mmol) in CH_3CN (2 mL) at r.t.
[b] Yield of the isolated product.
[c] The catalyst loading was 5 mol%.
[d] The catalyst loading was 20 mol%.

yields of 23% and 20%, respectively (entries 12 and 13). The yield also clearly dropped on decreasing the catalyst loading (entry 14). In contrast, a higher catalyst loading did not result in an improvement in the yield (entry 15). Thus, the optimal conditions were established to be as follows: phenylhydrazine (0.5 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (10 mol%), dione **2** (0.6 mmol) in CH_3CN for one hour at room temperature.

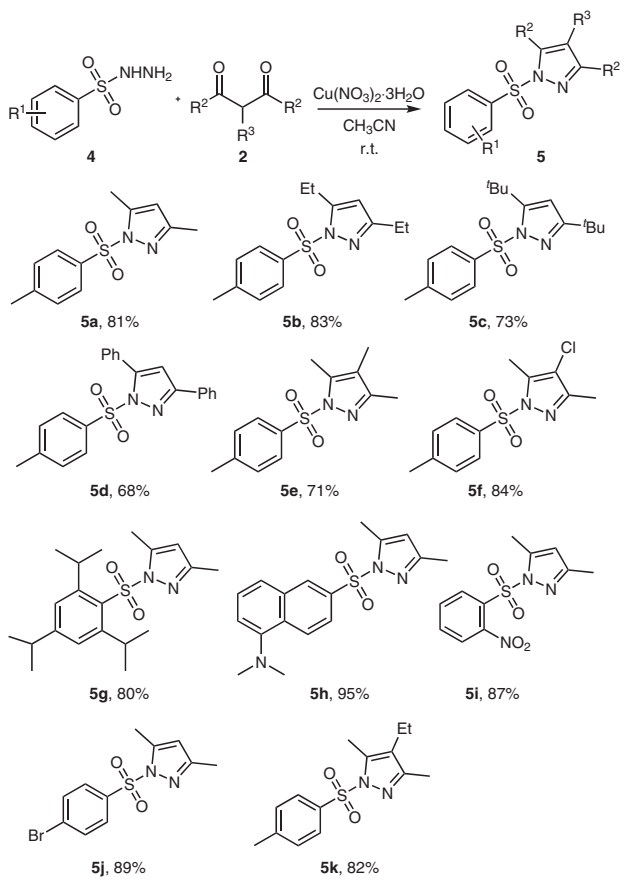
With optimal conditions established, we focused on the scope and generality of this copper-catalyzed condensation reaction by examining the reactions of a variety of substituted 2,4-diones and substituted phenylhydrazines in the presence of 10 mol% $Cu(NO_3)_2{\cdot}3H_2O$ in CH_3CN (2 mL) at room temperature.[10] The results are outlined in Scheme 1. To investigate the factors that control the reaction, the effects of dione substituents R^2 and R^3 with various electronic and steric properties were examined. A range of diones **2a–e** and **2n** gave the expected pyrazoles **3a–e** and **3n**, respectively, in moderate to excellent yields under the standard reaction conditions. Various electron-donating and electron-withdrawing functional groups on the phenyl ring, including Br, Cl, NO_2, CH_3, OCH_3 and 4-benzyloxy groups, were also tolerated (**3f–m**).



Scheme 1 The substrate scope of Cu-catalyzed synthesis of pyrazoles from various arylhydrazines and diones. *Reaction conditions*: arylhydrazine **1** (0.5 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (0.05 mmol), dione **2** (0.6 mmol), CH_3CN (2 mL), r.t., 1 h.

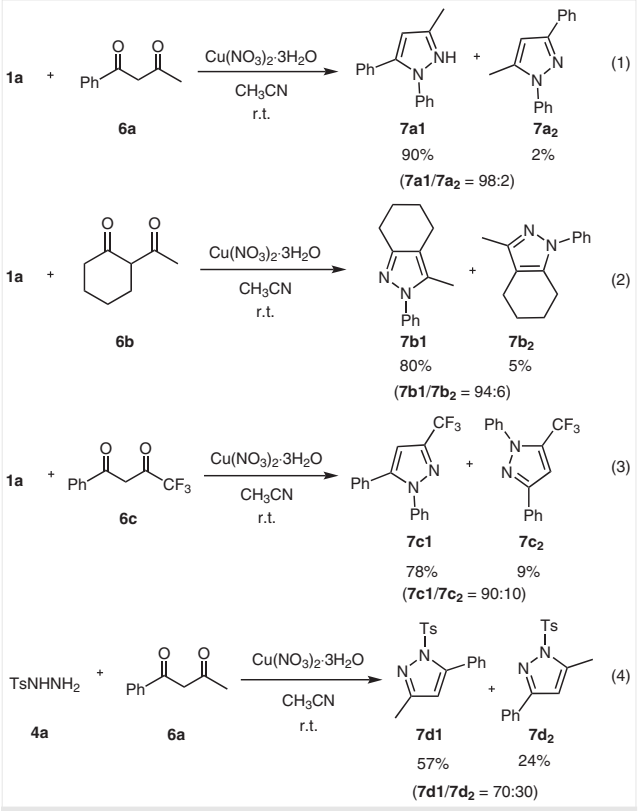
Inspired by the success of the formation of substituted pyrazoles from substituted phenylhydrazines, the scope of this Cu-catalyzed synthesis of substituted pyrazoles was further explored by examining the reactions of sulfonyl hydrazides **4** with various diones (Scheme 2).[11] The transformations proceeded smoothly to afford the corresponding N-substituted pyrazoles **5a**, **5b**, and **5d** in good to excellent yields. Good yields of **5e**, **5f**, and **5k** were also obtained when the R^3 substituent in the diketone was replaced by a methyl, ethyl, or Cl group, respectively. Similarly, sulfonyl hydrazide containing an *ortho*-nitro or a *para*-bromo substituent on the aromatic ring gave the corresponding pyrazoles **5i** and **5j** in excellent yields. The enhanced reactivity of sulfonyl hydrazides was proven by comparison with the copper-catalyzed condensation reaction of arylhydrazines. The reaction was completed within 15 minutes when a

copper catalyst was used. Remarkably, the sterically hindered *tert*-butyl-substituted dione **2c** and the isopropyl-substituted sulfonyl hydrazide **2g** were also well tolerated in this reaction, providing the desired products **5c** and **5g** in 73% and 80% yield, respectively. This result showed that steric effects in the dione or sulfonyl hydrazide had little influence on this reaction. Notably, product **5h** containing a naphthyl group was also successfully prepared in 95% yield.



Scheme 2 Substrate scope of Cu-catalyzed synthesis of pyrazoles from various sulfonyl hydrazides and diones. *Reaction conditions*: sulfonyl hydrazide **4** (0.5 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (0.05 mmol), dione **2** (0.6 mmol), CH_3CN (2 mL), 15 min, r.t.

Compared with symmetrical diones, unsymmetrical diones are much more challenging substrates due to the difficulty in controlling the regioselectivity of the reaction (Scheme 3). Pleasingly, unsymmetrical diones also performed well with our catalyst system, and were successfully converted into the corresponding substituted pyrazoles with excellent yields and regioselectivities [Scheme 3, equations (1) and (2)]. A fluorinated dione was also successfully employed in the condensation reaction, with satisfactory results [Scheme 3, equation (3)]. However, *p*-toluenesulfonyl hydrazide (**4a**) gave two isomers $\mathbf{7d_1}$ and $\mathbf{7d_2}$ in yields of 57% and 24% and a ratio of 70:30 [Scheme 3, equation (4)]. Furthermore, **4a** failed to react with dione **6c** to provide the corresponding product, mainly as a result of the presence of a strongly electron-withdrawing substituent (CF_3).



Scheme 3 Substrate scope of Cu-catalyzed synthesis of pyrazoles from unsymmetrical diones. *Reaction conditions*: phenylhydrazine (0.5 mmol) or $TsNHNH_2$ (0.5 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (0.05 mmol), unsymmetrical dione **6** (0.6 mmol), CH_3CN (2 mL), r.t.

In conclusion, we have developed a copper-catalyzed procedure for the synthesis of substituted pyrazoles under acid-free conditions at room temperature. The reaction is general with good functional-group compatibility, giving the corresponding substituted pyrazoles in good to excellent yields in short reaction times. This synthetic method offers a convenient, practical, and economical approach to the synthesis of the structurally important pyrazole skeleton for biological research and drug discovery. Further development of this approach and application of the reaction system to other reaction manifolds is currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610330.

References and Notes

(1) (a) McDonald, E.; Jones, K.; Brough, P. A.; Drysdale, M. J.; Workman, P. *Curr. Top. Med. Chem.* **2006**, *6*, 1193. (b) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst.* **2002**, *6*, 52. (c) Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819. (d) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Ed.; Pergamon: Oxford, **1996**, 1. (e) Keter, F. K.; Darkwa, J. *BioMetals* **2012**, *25*, 9. (f) Havrylyuk, D.; Zimenkovsky, B.; Vasylenko, O.; Gzella, A.; Lesyk, R. *J. Med. Chem.* **2012**, *55*, 8630. (g) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984.

(2) (a) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Chem. Educ.* **2013**, *90*, 1403. (c) Bekhit, A. A.; Abdel-Aziem, T. *Bioorg. Med. Chem.* **2004**, *12*, 1935. (d) Selvam, C.; Jachak, S. M.; Thilagavathi, R.; Chakraborti, A. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1793.

(3) (a) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2597. (b) Wang, Z.-X.; Qin, H.-L. *Green Chem.* **2004**, *6*, 90. (c) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: Oxford, **1985**, 416. (d) Hayter, M. J.; Bray, D. J.; Clegg, J. K.; Lindoy, L. F. *Synth. Commun.* **2006**, *36*, 707. (e) Sanchez-Carmona, M. A.; Contreras-Cruz, D. A.; Miranda, L. D. *Org. Biomol. Chem.* **2011**, *9*, 6506. (f) Vaddula, B. R.; Varma, R. S.; Leazer, J. *Tetrahedron Lett.* **2013**, *54*, 1538. (g) Zakerinasab, B.; Nasseri, M. A.; Hassani, H.; Samieadel, M. M. *Res. Chem. Intermed.* **2016**, *42*, 3169. (h) Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2008**, *49*, 397.

(4) Shao, N.; Chen, T.; Zhang, T.; Zhu, H.; Zheng, Q.; Zou, H. *Tetrahedron* **2014**, *70*, 795.

(5) Zhang, H.; Wei, Q.; Zhu, G.; Qu, J.; Wang, B. *Tetrahedron Lett.* **2016**, *57*, 2633.

(6) Hu, J.; Chen, S.; Sun, Y.; Yang, J.; Rao, Y. *Org. Lett.* **2012**, *14*, 5030.

(7) (a) McLaughlin, M.; Marcantonio, K.; Chen, C.-y.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 4309. (b) Dishington, A.; Feron, J. L.; Gill, K.; Graham, M. A.; Hollingsworth, I.; Pink, J. H.; Roberts, A.; Simpson, I.; Tatton, M. *Org. Lett.* **2014**, *16*, 6120.

(8) (a) Vanjari, R.; Guntreddi, T.; Kumar, S.; Singh, K. N. *Chem. Commun.* **2015**, *51*, 366. (b) Wen, J.-J.; Tang, H.-T.; Xiong, K.; Ding, Z.-C.; Zhan, Z.-P. *Org. Lett.* **2014**, *16*, 5940. (c) Yu, X.; Huang, N.; Feng, X.; Yamamoto, Y.; Bao, M. *Synthesis* **2014**, *46*, 2422.

(9) (a) Stoit, A. R.; Lange, J. H. M.; den Hartog, A. P.; Ronken, E.; Tipker, K.; van Stuivenberg, H. H.; Dijksman, J. A. R.; Wals, H. C.; Kruse, C. G. *Chem. Pharm. Bull.* **2002**, *50*, 1109. (b) Chen, X.; She, J.; Shang, Z.-C.; Wu, J.; Zhang, P. *Synth. Commun.* **2009**, *39*, 947. (c) Gosselin, F.; O'Shea, P. D.; Webster, R. A.; Reamer, R. A.; Tillyer, R. D.; Grabowski, E. J. J. *Synlett* **2006**, 3267. (d) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675. (e) Kumar, S. V.; Yadav, S. K.; Raghava, B.; Saraiah, B.; Ila, H.; Rangappa, K. S.; Hazra, A. *J. Org. Chem.* **2013**, *78*, 4960. (f) Rosa, F. A.; Machado, P.; Vargas, P. S.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Synlett* **2008**, 1673. (g) Ma, C.; Li, Y.; Wen, P.; Yan, R.; Ren, Z.; Huang, G. *Synlett* **2011**, 1321. (h) Martín, R.; Rodríguez Rivero, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079.

(10) **3,5-Dimethyl-1-phenyl-1*H*-pyrazole (3a); Typical Procedure**
$Cu(NO_3)_2 \cdot 3\ H_2O$ (10 mol%) was added to a stirred solution of $PhNHNH_2$ (**1a**; 0.5 mmol) and pentane-2,4-dione (**2**; 0.6 mmol) in CH_3CN (2 mL) at r.t., and the resulting solution was stirred at r.t. for 1 h. When the reaction was complete, the mixture was concentrated to remove MeCN, and the residue was dissolved in CH_2Cl_2 (30 mL). The organic layer was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography [silica gel, PE–EtOAc (20:1)] to give a colorless oil; yield: 75 mg (87%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.40 (m, 4 H), 7.36–7.32 (m, 1 H), 6.01 (s, 1 H), 2.32 (s, 3 H), 2.31 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.94, 139.99, 139.35, 128.98, 127.21, 124.75, 106.94, 13.53, 12.37. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2$: 173.1073; found: 173.1074.

(11) **3,5-Dimethyl-1-tosyl-1*H*-pyrazole (5a); Typical Procedure**
Pentane-2,4-dione (**2**; 0.6 mmol) and $Cu(NO_3)_2 \cdot 3H_2O$ (10 mol%) were added to a round-bottomed flask containing a solution of $TsNHNH_2$ (**4a,** 0.5 mmol) in CH_3CN (2 mL), and the mixture was stirred for 15 min. The mixture was then concentrated to remove MeCN, and the residue was dissolved in CH_2Cl_2 (30 mL). The organic layer was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography [silica gel, PE–EtOAc (20:1)] to give a white solid; yield 101 mg (81%); mp 97–98 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.3 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 5.90 (s, 1 H), 2.49 (s, 3 H), 2.41 (s, 3 H), 2.20 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.46, 145.22, 144.15, 135.48, 129.96, 127.63, 110.81, 21.71, 13.90, 13.16. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2S$: 251.0849; found: 251.0846.