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Iron(III) Chloride/L-Proline as an Efficient Catalyst for the Synthesis of 3-Substituted 1,2,4-Oxadiazoles from Amidoximes and Triethyl Orthoformate

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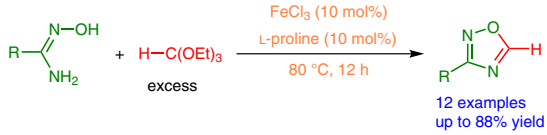

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Abstract A general, facile, and efficient method is presented for the synthesis of 3-substituted 1,2,4-oxadiazoles from amidoximes and triethyl orthoformate. The procedure employs an iron(III) chloride/L-proline catalytic system and the 3-substituted 1,2,4-oxadiazole products are obtained in moderate to good yields.

Key words 1,2,4-oxadiazoles, iron(III) chloride, L-proline, amidoximes, triethyl orthoformate

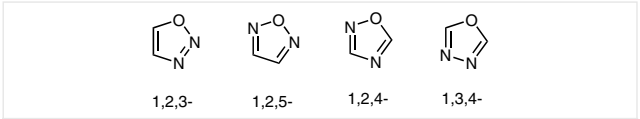


Figure 1 Structures of oxadiazoles

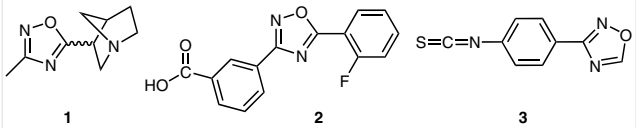
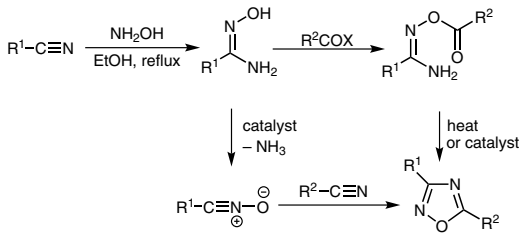


Figure 2 Examples of drugs containing a 1,2,4-oxadiazole ring: muscarinic receptor for the treatment of Alzheimer's (**1**), Duchenne muscular dystrophy and potentially other genetic disorders (**2**) (Ataluren), and helminthiasis (**3**)

The chemistry of heterocyclic compounds is an important research area in organic chemistry due to their use in pharmaceuticals and their presence in natural products as well as new materials. Oxadiazoles are five-membered heterocyclic compounds that occupy a special place due to the growing importance of these heterocycles for the design of biologically active compounds and for materials construction.[1] Among oxadiazoles, 1,2,4-oxadiazoles are particularly important (Figure 1).[2,3] They function as hydrolytically stable bioisosteres for esters or amides showing biological properties as antidiabetic,[4] anti-inflammatory,[5] antimicrobial,[6] antitumor,[7] anticonvulsant,[8] and neuroprotective[9] agents. 1,2,4-Oxadiazoles are also found in several drugs including muscarinic receptor agonists for the treatment of Alzheimer's disease,[10] Duchenne muscular dystrophy and potentially other genetic disorders,[11] and helminthiasis[12] (Figure 2).

The most common routes for the synthesis of 1,2,4-oxadiazoles are shown in Scheme 1.[13–15] In general, 1,2,4-oxadiazoles are prepared by heterocyclization of O-acylated amidoximes derived from an active acyl chloride and amidoximes (Scheme 1).[16] Heterocyclization can be effected by treating an *O*-acylamidoxime with bases such as NaH or NaOEt at room temperature, or pyridine with heating.[17] 1,2,4-Oxadiazoles are also prepared by [3+2]-cycloaddition of nitrile oxides with nitriles.[18] In contrast to the widely studied 3,5-disubstituted 1,2,4-oxadiazoles, relatively few papers have been reported on the synthesis of 3-monosubstituted 1,2,4-oxadiazoles.

3-Monosubstituted 1,2,4-oxadiazoles are prepared by the reaction of amidoximes with ethyl orthoformate at high temperature.[19] Recently, Makhova et al. reported scandium triflate as an efficient catalyst for the synthesis of 3-methyl-4-(1,2,4-oxadiazol-3-yl)furoxan via tandem reaction of furoxanylamidoxime with a trialkyl orthoformate at ambient temperature.[20] However, to the best our knowledge, there is



Scheme 1 Different methods for the synthesis of 1,2,4-oxadiazoles

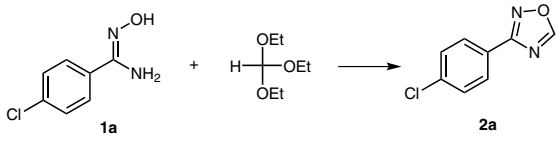
no report of a general method for the synthesis of 3-monosubstituted 1,2,4-oxadiazoles via the reaction of amidoximes with triethyl orthoformate.

Therefore, it is highly desirable to develop novel, simple and mild methods for the synthesis of 3-monosubstituted 1,2,4-oxadiazoles. In this study, we report an efficient $FeCl_3$/L-proline catalyzed condensation and cyclization of amidoximes with triethyl orthoformate for the synthesis of 3-monosubstituted 1,2,4-oxadiazoles.

Initially, the one-pot reaction of 4-chlorobenzamidoxime (**1a**) (1 equiv) with triethyl orthoformate (1 equiv) was chosen as a model reaction to be studied under various reaction conditions, and the results are summarized in Table 1. Treatment of **1a** with triethyl orthoformate (1 equiv) in DMF at 80 °C in the absence of any catalyst gave the corresponding oxadiazole **2a** in 12% yield after 24 hours (Table 1, entry 1). In toluene and DMSO (Table 1, entries 2 and 3), the reaction failed to give the corresponding adduct **2a** after 24 hours at 80 °C, while the yield increased to only 18% at reflux temperature in ethanol (Table 1, entry 4).

Treatment of **1a** with triethyl orthoformate (excess) under solvent-free conditions at 80 °C for 24 hours gave **2a** in only 21% yield (Table 1, entry 5), and the same reaction proceeded only marginally better under solvent-free conditions at reflux temperature for 24 hours to give **2a** in 27% yield (Table 1, entry 6). While treatment of **1a** with triethyl orthoformate (excess) for 24 hours gave **2a** in only 35% yield in the presence of triethylamine as a basic catalyst (Table 1, entry 7), further experiments on the same reaction in the presence of different bases (Table 1, entries 8–10) revealed that the reaction did not give satisfactory results. After screening several bases, the effects of various Lewis acid catalysts on oxadiazole formation were also investigated (Table 1, entries 11–17). There was no reaction when $ZnCl_2$ was used as the catalyst, while employing $HgCl_2$ or $FeCl_3$ resulted in yields of **2a** of only 35% and 51%, respectively (Table 1, entries 11–13). Interestingly, when the reaction was conducted with $FeCl_3$/phenanthroline (0.2 equiv of each) or $FeCl_3$/L-proline, the oxadiazole **2a** was obtained in 90% yield (Table 1, entries 14 and 15). Compared to phenanthroline, L-proline is much cheaper, non-toxic and is more readily available, and it was therefore selected as the ligand for the catalytic preparation of oxadiazoles. Further, the effect of the amount of $FeCl_3$/L-proline and the reaction temperature was investigated (Table 1, entries 16–19). The results indicated that decreasing the amount of catalyst (0.1 equiv of each) did not lead to a significant decrease in the yield of **2a** (Table 1, entry 16). Similarly, decreasing the reaction time from 24 to 12 hours resulted in only a slight decrease in the yield of the oxadiazole. Decreasing the reaction temperature (from 80 °C to 50 °C) or the amount of catalyst (0.05 equiv of each) resulted in lower yields of **2a** (Table 1, entries 18 and 19). Thus, the optimum reaction conditions for the synthesis of oxadiazole **2a** involved the use of 0.1 equiv of $FeCl_3$/L-proline at 80 °C for 12 hours.

Table 1 Reaction of 4-Chlorobenzamidoxime (**1a**) with Triethyl Orthoformate[a]

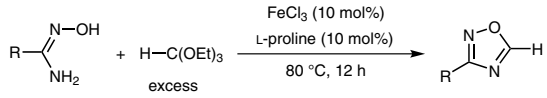


Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	–	DMF	80	24	12
2	–	toluene	80	24	–
3	–	DMSO	80	24	–
4	–	EtOH	reflux	24	18
5	–	–[c]	80	24	21
6	–	–[c]	reflux	48	27
7	Et_3N	–[c,d]	80	24	35
8	K_2CO_3	–[c,d]	80	24	20
9	KF	–[c,d]	80	24	21
10	$(NH_4)_2CO_3$	–[c,d]	80	24	30
11	$ZnCl_2$	–[c,e]	80	24	–
12	$HgCl_2$	–[c,e]	80	24	35
13	$FeCl_3$	–[c,e]	80	24	51
14	$FeCl_3$/phenanthroline	–[c,e]	80	24	90
15	$FeCl_3$/L-proline	–[c,e]	80	24	90
16	$FeCl_3$/L-proline	–[c,f]	80	24	89
17	$FeCl_3$/L-proline	–[c,f]	80	12	87
18	$FeCl_3$/L-proline	–[c,f]	50	12	68
19	$FeCl_3$/L-proline	–[c,g]	80	12	73

[a] Amidoxime (1 equiv) and triethyl orthoformate (1 equiv) were used unless otherwise noted.
[b] Yield of isolated product.
[c] Excess triethyl orthoformate was used.
[d] In the presence of a base (1 equiv).
[e] In the presence of a Lewis acid (0.2 equiv).
[f] In the presence of $FeCl_3$/L-proline (0.1 equiv of each).
[g] In the presence of $FeCl_3$/L-proline (0.05 equiv of each).

To explore the scope of the synthesis of 3-monosubstituted 1,2,4-oxadiazoles, we applied this protocol to a range of amidoximes. The methodology proved suitable for the synthesis of 3-monosubstituted 1,2,4-oxadiazoles in moderate to good yields as shown in Table 2.

Table 2 Reactions of Amidoximes **1** with Triethyl Orthoformate in the Presence of $FeCl_3$/L-Proline[a]



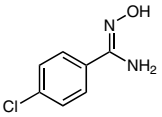
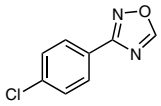
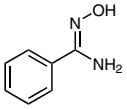
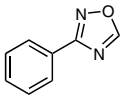
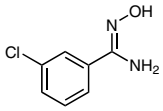
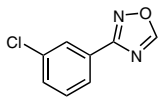
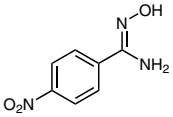
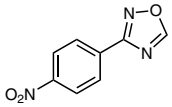
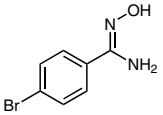
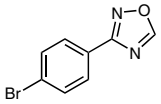
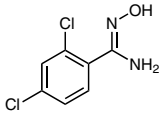
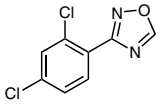
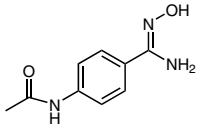
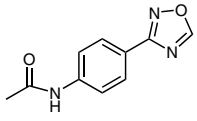
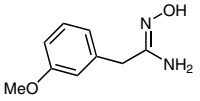
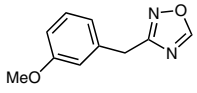
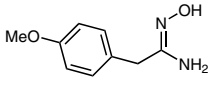
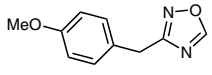
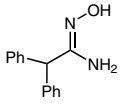
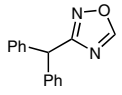
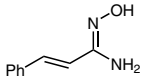
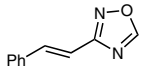
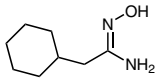
Entry	Amidoxime	Oxadiazole		Yield (%)[b]
1			**2a**	87
2			**2b**	83
3			**2c**	73
4			**2d**	51
5			**2e**	88
6			**2f**	72
7			**2g**	47
8			**2h**	45
9			**2i**	32

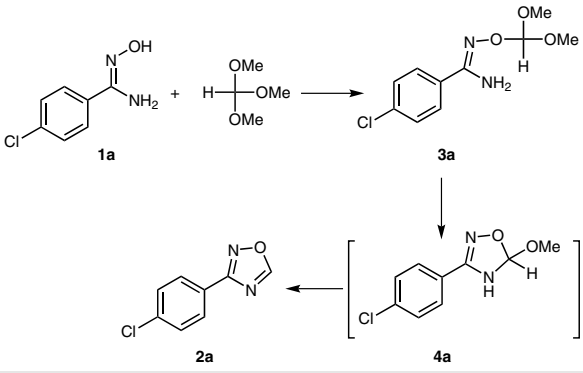
Table 2 (continued)

Entry	Amidoxime	Oxadiazole		Yield (%)[b]
10			**2j**	20
11			**2k**	45
12		–	–	–[c]

[a] Amidoxime (1 equiv), triethyl orthoformate (excess) and $FeCl_3$/L-proline (10 mol%) were used.
[b] Yield of isolated product after column chromatography.
[c] No reaction.

Substituted benzamidoximes reacted with triethyl orthoformate in the presence of 10 mol% of $FeCl_3$/L-proline to afford the desired products **2b**–**g** in moderate to good yields (Table 2, entries 2–7). Benzylamidoximes **1h**–**j** also reacted with triethyl orthoformate to give the corresponding oxadiazoles **2h**–**j** (Table 2, entries 8–10). The process was also successfully applied to unsaturated amidoxime **1k** and the desired product **2k** was obtained in 45% isolated yield (Table 2, entry 11). However, treatment of cyclohexylamidoxime **1l** with triethyl orthoformate under the same conditions failed to give the expected 1,2,4-oxadiazole (Table 2, entry 12).

Next, we used trimethyl orthoformate for the synthesis of oxadiazoles from amidoximes in the presence of $FeCl_3$/L-proline (10 mol%). Similar treatment of **1a** with trimethyl orthoformate (excess) at 80 °C gave the corresponding oxadiazole **2a** in 86% yield after 12 hours (Scheme 2).

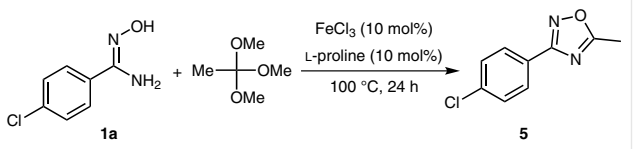


Scheme 2 Proposed mechanism for the synthesis of oxadiazoles

When the reaction carried out for six hours, intermediate **3a** was separated from the reaction mixture and characterized by NMR spectroscopy. A proposed mechanism is

outlined in Scheme 2 for the synthesis of oxadiazoles **2**. The present process is thought to proceed via the reaction of amidoxime **1a** with trimethyl orthoformate to give intermediate **3a**, followed by internal cyclization to give the oxadiazole **2a**.

We found that it was also possible to carry out this reaction with trimethyl orthoacetate to give the corresponding oxadiazole **5** in 87% isolated yield (Scheme 3).



Scheme 3 Reaction of 4-chlorobenzamidoxime **1a** (1 equiv) with trimethyl orthoacetate (excess) in the presence of $FeCl_3$/L-proline

In conclusion, we have reported a simple and convenient method for the synthesis of 3-monosubstituted 1,2,4-oxadiazoles via the reaction of amidoximes with triethyl orthoformate in the presence of 10 mol% of $FeCl_3$/L-proline. The simple work-up, mild reaction conditions, moderate to good yields, and clean reactions should make this method an attractive and useful contribution to present methodologies.

All chemicals were commercial products and were distilled or recrystallized before use. Silica gel column chromatography was carried out with silica gel 100 (Merck No. 10184). Merck silica gel 60 F254 plates (No. 5744) were used for preparative TLC. Melting points are uncorrected. NMR spectra were recorded with a 400 MHz Bruker Avance instrument with the chemical shifts (δ) being reported in ppm and coupling constants expressed in Hz. Elemental analysis was performed using an Elementar Vario EL III analyzer.

Amidoximes 1; General Procedure

The amidoximes were prepared according to our previous report.[16h] To a solution of the appropriate nitrile (0.01 mol) in EtOH (200 mL) was added a solution of hydroxylamine hydrochloride (0.695 g, 0.01 mol) in H_2O (10 mL), followed by the addition of Na_2CO_3 (0.420 g, 0.005 mol) in H_2O (10 mL). The reaction was stirred overnight at r.t. and then concentrated to a small volume under vacuum, diluted with cold H_2O, and placed in a refrigerator overnight. The precipitate that formed was recovered and recrystallized from EtOH. All the prepared amidoximes are known and were characterized by comparison of their physical data with those prepared in accordance with literature procedures.

3-Monosubstituted 1,2,4-Oxadiazoles 2; General Procedure

Triethyl orthoformate (4 mL) was added to a mixture of $FeCl_3$ (9–10 mg, 0.05 mmol), L-proline (5–6 mg, 0.05 mmol) and Et_3N (0.014 mL, 0.1 mmol), and the resulting solution was stirred for 1 h at ambient temperature. The amidoxime **1** (1 mmol) was added and the mixture was stirred at 80 °C for 12 h. After cooling, the reaction mixture was washed with Et_2O (3 × 10 mL). The organic layer was dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography on silica gel (EtOAc–*n*-hexane, 5:95) and evaporation of the solvent under reduced pressure gave pure products in 20–88% isolated yields. All products gave satisfactory spectral data in accordance with the assigned structures.

3-(4-Chlorophenyl)-1,2,4-oxadiazole (2a)

Yield: 155 mg (87%); mp 97–98 °C (Lit.[19] 100–103 °C); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.0 Hz, 2 H), 8.08 (d, *J* = 8.0 Hz, 2 H), 8.78 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.8, 128.9, 129.3, 137.6, 164.9, 167.0.

3-Phenyl-1,2,4-oxadiazole (2b)[19]

Yield: 120 mg (83%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.59 (m, 3 H), 8.12–8.19 (m, 2 H), 8.71 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.3, 127.6, 128.9, 130.4, 164.8, 167.8.

3-(3-Chlorophenyl)-1,2,4-oxadiazole (2c)

Yield: 130 mg (73%); mp 43–45 °C (Lit.[19] 42 °C); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.55 (m, 2 H), 8.04 (dd, J_1 = 7.6, J_2 = 1.2 Hz, 1 H), 8.14–8.16 (m, 1 H), 8.81 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 125.6, 127.7, 127.9, 130.3, 131.5, 135.0, 165.0, 166.8.

3-(4-Nitrophenyl)-1,2,4-oxadiazole (2d)

Yield: 97 mg (51%); mp 148–151 °C (Lit.[21] 162–164 °C); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.8 Hz, 2 H), 8.39 (d, *J* = 8.0 Hz, 2 H), 8.88 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.2, 128.6, 132.1, 149.6, 165.4, 166.3.

3-(4-Bromophenyl)-1,2,4-oxadiazole (2e)

Yield: 196 mg (88%); mp 107–110 °C (Lit.[19] 110 °C); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.4 Hz, 2 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 8.79 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 125.2, 126.9, 129.0, 132.3, 164.9, 167.1.

3-(2,4-Dichlorophenyl)-1,2,4-oxadiazole (2f)

Yield: 154 mg (72%); mp 79–81 °C; white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.4 Hz, 1 H), 7.62 (s, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 8.86 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.1, 127.7, 131.5, 132.6, 134.4, 137.6, 164.3, 165.9.

Anal. Calcd for $C_8H_4N_2Cl_2O$: C, 44.86; H, 1.88; N, 13.09. Found: C, 45.12; H, 2.15; N, 13.05.

N-[4-(1,2,4-Oxadiazol-3-yl)phenyl]acetamide (2g)

Yield: 95 mg (47%); mp 99–101 °C (Lit.[22] 142–143 °C); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 7.43 (d, *J* = 6.8 Hz, 2 H), 8.05 (d, *J* = 6.8 Hz, 2 H), 9.33 (s, 1 H), 9.47 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 119.1, 128.1, 142.4, 159.1, 166.2, 168.6, 205.5.

3-(3-Methoxybenzyl)-1,2,4-oxadiazole (2h)

Yield: 86 mg (45%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 4.13 (s, 2 H), 6.83 (dd, J_1 = 2.0, J_2 = 8.0 Hz, 1 H), 6.90 (d, J = 2.0 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 7.27 (t, J = 8.0 Hz, 1 H), 8.65 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.1, 55.2, 112.8, 114.8, 121.3, 129.8, 136.6, 159.9, 164.9, 168.7.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.27; N, 14.65. Found: C, 63.10; H, 5.15; N, 14.38.

3-(4-Methoxybenzyl)-1,2,4-oxadiazole (2i)[23]

Yield: 60 mg (32%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 4.11 (s, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.27 (d, J = 8.8 Hz, 2 H), 8.64 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 55.3, 114.2, 127.2, 130.1, 158.8, 164.8, 169.1.

3-Benzhydryl-1,2,4-oxadiazole (2j)

Yield: 47 mg (20%); mp 93–94 °C; white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (s, 1 H), 7.29–7.38 (m, 10 H), 8.72 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.4, 127.4, 128.7, 128.8, 139.4, 164.9, 171.0.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.24; H, 5.12; N, 11.86. Found: C, 76.50; H, 5.18; N, 11.58.

3-Styryl-1,2,4-oxadiazole (2k)

Yield: 77 mg (45%); mp 80–82 °C (Lit.[24] 82 °C); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 16.0 Hz, 1 H), 7.35–7.50 (m, 3 H), 7.61 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 16.0 Hz, 1 H), 8.70 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.0, 127.5, 128.9, 129.6, 135.1, 139.7, 164.0, 167.1.

3-(4-Chlorophenyl)-5-methyl-1,2,4-oxadiazole (5)

Yield: 170 mg (87%); mp 93–94 °C (Lit.[25] 92–95 °C); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 3 H), 7.50 (d, J = 8.0 Hz, 2 H), 8.05 (d, J = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 125.3, 128.7, 129.2, 137.3, 167.6, 176.8.

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