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An efficient one-pot synthesis of 3-aryl-5-methylisoxazoles from aryl aldehydes

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Dedicated with affection to Professor Theodore Cohen of University of Pittsburgh on the occasion of his 80th birthday

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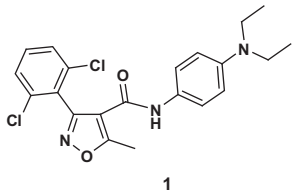
ABSTRACT

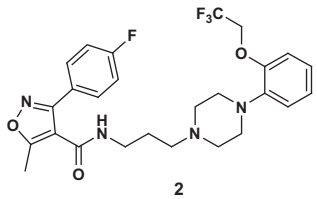
An efficient protocol for the one-pot preparation of alkyl 3-aryl-5-methylisoxazole-4-carboxylates from aryl aldehydes is described. This method is readily amenable to the large scale preparation of isoxazoles as well as the parallel synthesis of isoxazole libraries.

1. Introduction

Isoxazole derivatives have been widely studied as potential pharmaceutical agents.[1] For example, structures containing the 3-aryl-5-methylisoxazole-4-carboxamide moiety have been reported as modulators of the ghrelin receptor (**1**),[2] selective antagonists of the α_{1a} adrenergic receptor (**2**),[3] and allosteric metabotropic glutamate receptor **7** antagonists (isoxazolopyridone **3** was prepared from **4** in two steps).[4] Isoxazoles have also served as versatile building blocks in organic synthesis.[5]



1



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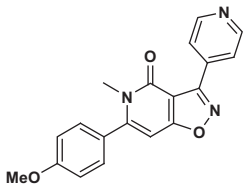

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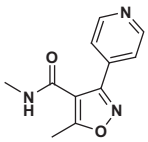

4

A frequently-cited and robust synthetic route to 3-aryl-5-methylisoxazole carboxylates is the 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxides.[5b] This procedure involves three discrete steps: (1) conversion of an aldehyde to the corresponding oxime; (2) α-chlorination of the oxime using *N*-chlorosuccinimide (NCS), usually initiated by HCl gas; and (3) reaction of the resulting hydroximinoyl chloride with a dipolarophile such as an alkyne,[6] the enolate of a β-ketoester or β-ketoamide[7] or the enamine of a β-ketoester.[8] As shown in Scheme 1 for the reaction with the enamine of a β-ketoester, a different solvent (or solvent mixture) is used in each of the three reactions: (1) water/ethanol; (2) DMF; and (3) ethanol. In practice, the oxime and hydroximinoyl chloride intermediates are usually isolated via extraction and used in the next step without further purification. Although this three-step procedure is quite general, we found that the chemistry was not amenable to the parallel synthesis of libraries of isoxazoles due to the number of extraction, filtration, and solvent evaporation steps. We sought a one-pot procedure to overcome these limitations.

Our initial breakthrough in this effort was the discovery that the final step (dipolar cycloaddition) could be carried out in an EtOH/DMF solvent mixture. This allowed us to combine the chlorination and the 1,3-dipolar cycloaddition steps and eliminate the isolation of hydroximinoyl chlorides from DMF. Our standard procedure involved adding a solution of the enamine of ethyl acetoacetate and triethylamine in ethanol to the chlorination reaction mixture.[9] Further efficiency was gained by generating the oximes in DMF rather than an ethanol/water mixture. In order to promote oxime formation, it was necessary to add triethylamine to the mixture of

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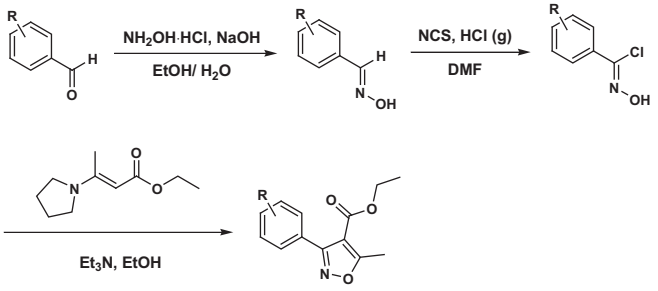
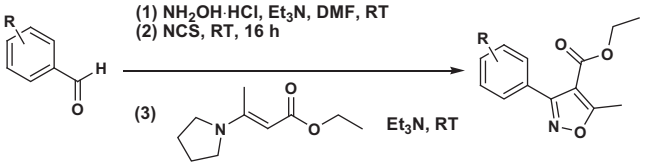


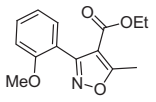
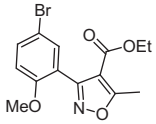
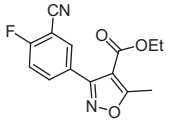
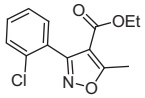
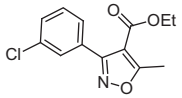
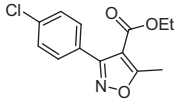
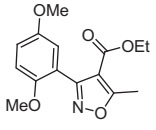
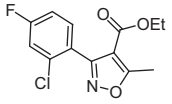
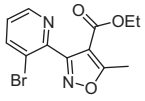
Scheme 1.

aldehyde and hydroxylamine hydrochloride in DMF. These solvent changes provided an efficient one-pot synthesis of isoxazoles from aldehydes (Eq. 1). The oxime-forming step is usually complete within 1 h at room temperature. The chlorination was done by simply adding *N*-chlorosuccinimide all at once to the oxime reaction mixture. It is not necessary to add NCS slowly in portions or use HCl gas or heat[10] to initiate the reaction and the chlorination is complete overnight. We generally use a slight excess of NCS to drive the chlorination step to completion. Finally, a solution of the enamine of ethyl acetoacetate and triethylamine in ethanol was added. The 1,3-dipolar cycloaddition can take from 2 to 16 h. All three reaction steps can be conveniently monitored by LC/MS. The overall yield of isoxazoles generated in the one-pot synthesis is usually higher than the yield obtained via the three-step procedure described previously. This is exemplified by direct comparison of the yield of the same isoxazoles (compounds **1**, 4 and **5**) synthesized by our one-pot method and that reported in Ref. [8b]. We have achieved yields very similar to those reported in the literature when we carried out the synthesis following the three-step procedure.



(1)

Table 1
Isoxazoles prepared from aldehydes by one-pot synthesis

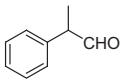
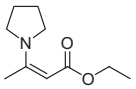
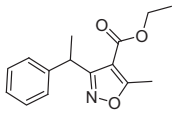
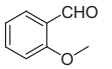
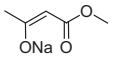
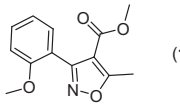
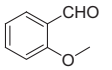
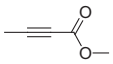
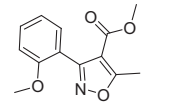
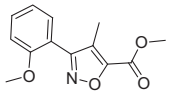
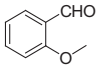
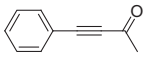
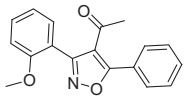
Compd No.	Structure of product	Yield (%)[a] of one-pot syn.	Yield (%) of multi-step syn.	Purity (%)
1		93[b]	40[d], (100,78,51)	98.1
2		84[c]		99.2
3		79[c]		99.3
4		90	68[d], (96,94,75)	99.6
5		79	47[d], (69, 90,75)	99.0
6		69		98.3
7		60		99.7
8		67		99.4
9		85		98.5

[a] Isolated yields for products purified by preparative HPLC unless noted otherwise.
[b] Yield of crude product.
[c] Products purified by flash chromatography.
[d] Yields for individual steps in parentheses as reported in Ref. 8b.

At a small scale as 50–100 mg, this one-pot synthesis can be easily carried out at room temperature in glass vials sealed with Teflon caps. The products are purified by preparative HPLC by injecting the reaction mixture. For reactions with precipitate in the reaction mixture, we can either add small amount of water to make a clear solution, or filter to remove the precipitate prior to injection for purification. Consistently good yields were observed for all isoxazoles synthesized in the library format.

With minor modifications, this one-pot synthesis was carried out at a scale greater than 10 g of product. We have observed that the oxime formation and the chlorination steps are exothermic. Therefore, triethylamine was added dropwise as a solution in DMF and both triethylamine and NCS were added at 0 °C. For compound **1**, the product isolated by extraction is clean by NMR analysis. It was hydrolyzed to give the isoxazole carboxylic acid **10**, the desired product of our program. The isoxazole acid did not require purification other than extraction following the ester saponification step and the acid was even cleaner than its ester precursor. All products were characterized by HPLC (purity reported in Table 1) and NMR.[11] The new compounds were also characterized by high resolution mass spectrometry.

Table 2
Isoxazoles from aliphatic aldehydes or other dipolarophiles

Aldehyde	Dipolarophile	Products (compd No., %yield)
		 (**11**, 38%)
		 (**12**, 60%)
		 (**12**, 61%)
		 (**13**, 4%)
		 (**14**, 65%)

2. Representative procedures

2.1. Procedure for large scale synthesis

2.1.1. Ethyl 3-(2-methoxyphenyl)-5-methylisoxazole-4-carboxylate (1)

To the mixture of 2-methoxybenzaldehyde (7.18 g, 52.7 mmol) and hydroxylamine hydrochloride (3.66 g, 52.7 mmol) in a 1000-mL round bottomed flask was added 100 mL of DMF. The suspension was stirred at 0 °C while a solution of triethylamine (5.34 g, 52.7 mmol) in 35 mL of DMF was added dropwise. The ice-water bath was removed once the addition of triethylamine was finished and the reaction mixture was stirred at rt for 2 h. The reaction mixture was cooled to 0 °C, followed by the addition of NCS (7.04 g, 52.7 mmol). The reaction mixture was stirred overnight, while the temperature rose from 0 °C to rt slowly. A solution of (*E*)-ethyl 3-(pyrrolidin-1-yl)but-2-enoate (10.15 g, 55.4 mmol) and triethylamine (3.20 g, 31.6 mmol) in ethanol (50.0 mL) was added dropwise and the resulting reaction mixture was stirred at rt for 16 h. Water (400 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (4 × 150 mL). The combined organic extracts were washed with water (2 × 100 mL), and dried over anhydrous sodium sulfate. Solvent was evaporated to give 12.85 g of the product (93%, theoretical yield 13.78 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.36 (m, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.77 (s, 3H), 2.72 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17 4. 1, 162.2, 160.2, 157.5, 131.1, 130.3, 120.4, 118.4, 110.5, 110.2, 60 .3, 55.4, 13.9, 13.0.

2.2. Procedure for small scale synthesis

2.2.1. Ethyl 3-(4-chlorophenyl)-5-methylisoxazole-4-carboxylate (6)

To the mixture of 4-chlorobenzaldehyde (100 mg, 0.711 mmol) and hydroxylamine hydrochloride (49.4 mg, 0.711 mmol) in an 8-mL vial was added 1.5 mL of DMF, followed by the addition of triethylamine (0.099 mL, 0.711 mmol). The vial was capped and stirred at ambient temperature for 1 h. NCS (0.095 g, 0.711 mmol) was added and the reaction vial was capped and stirred at ambient temperature overnight. Additional 15 mg of NCS was added and the reaction continued for 6 h. A solution of (*E*)-ethyl 3-(pyrrolidin-1-yl)but-2-enoate (130 mg, 0.711 mmol) and triethylamine (0.059 mL, 0.427 mmol) in ethanol (0.9 mL) was added and the resulting reaction mixture was stirred at room temperature for 16 h. The product was purified by preparative HPLC (0.1% TFA, MeOH/H_2O) to give 148.1 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 2.75 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 161.8, 161.6, 136.0, 130.8 (s, 2C), 128.2 (s, 2C), 127.0, 108.4, 60.8, 14.0, 13.6.

2.3. Procedure for hydrolysis of the ethyl ester to carboxylic acid

2.3.1. 3-(2-Methoxyphenyl)-5-methylisoxazole-4-carboxylic acid (10)

The reaction mixture of ethyl 3-(2-methoxyphenyl)-5-methylisoxazole-4-carboxylate (12.85 g, 49.2 mmol) and sodium hydroxide (9.84 g, 246 mmol) in MeOH (100 mL) and water (10 mL) in a 500-mL round bottomed flask was stirred at 65 °C for 20 h. The reaction mixture was concentrated by removing methanol by rotary evaporation. The concentrated reaction mixture was transferred to a 500-mL separatory funnel with 150 mL of water and 100 mL of ether. Two layers were separated and the organic layer was discarded. The aqueous layer was acidified by adding concentrated HCl (26 mL). The product precipitated and was separated by filtration and dried under high vacuum.

The yield of the product, 10.63 g, is 93% for the hydrolysis and 86.4% from 2-methoxybenzaldehyde used in the previous step. ^{1}H NMR (400 MHz, CD_3OD) δ 7.49–7.42 (m, 1H), 7.33 (dd, J = 7.4, 1.6 Hz, 1H), 7.09–6.98 (m, 2H), 3.77 (s, 3H), 2.69 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 175.6, 165.1, 162.1, 159.4, 132.5, 131.1, 121.5, 119.6, 112.3, 111.9, 56.1, 13.0.

3. Broadening applications

To explore the scope and limitations of the methodology, we studied aliphatic aldehydes and other dipolarophiles, as illustrated in Table 2. Alkynes (1.2 equiv relative to aldehyde) were added with equimolar triethylamine in ethanol to the reaction mixture. Enolates also be used as the dipolarophile: sodium methoxide (1 equiv to aldehyde) in methanol was added to the reaction mixture prior to the addition of the enolate, which was prepared by mixing equimolar β-ketoester and sodium methoxide in methanol.

All other reaction conditions remained the same as described in Section 2.2.

Only one example in Table 2 provided a mixture of two regioisomers, and in that instance the regioselectivity was >15:1 in favor of the desired product. These preliminary results demonstrate that the one-pot approach can be used for the synthesis of isoxazoles with a variety of substitution patterns.

4. Conclusion

We have simplified the synthesis of isoxazoles from aldehydes by combining the formation of oximes, chlorination of the oximes and the 1,3-dipolar cycloaddition of the commonly used dipolarophiles with the nitrile oxides generated in situ by the reaction of the hydroximinoyl chlorides with triethyl amine into a one-pot reaction. We have found this procedure to be particularly useful in the parallel synthesis of libraries of isoxazole analogs. Significant time and cost savings were also achieved when we synthesized isoxazoles at a large scale.

Acknowledgment

We thank Weixu Zhai for useful discussion of some experimental details.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.104.

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9. While this manuscript was in preparation, we noticed a similar protocol under different reaction conditions Nakamura, M.; Kurihara, H.; Suzuki, G.; Mitsuya, M.; Ohkubo, M.; Ohta, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 726–729.
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11. Analytical data.
Spectral data for ethyl 3-(5-bromo-2-methoxyphenyl)-5-methylisoxazole-4-carboxylate (**2**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.49 (m, 2H), 6.83 (d, J = 8.5 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 2.72 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 161.9, 159.0, 156.7, 133.7, 133.0, 120.3, 112.4, 112.3, 110.1, 60.4, 55.7, 13.9, 13.0.
HRMS: calcd for $C_{14}H_{15}BrNO_4$, (MH^+) 340.0185, found 340.0179.
Spectral data for ethyl 3-(3-cyano-4-fluorophenyl)-5-methylisoxazole-4-carboxylate (**3**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 6.0, 2.0 Hz, 1H), 7.94 (ddd, J = 8.8, 5.0, 2.3 Hz, 1H), 7.31 (t, J = 8.7 Hz, 1H), 4.30 (q, J = 7.0 Hz, 2H), 2.77 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 165.1, 162.4, 161.4, 160.0, 136.3, 136.2, 125.9, 116.4, 116.2, 113.3, 108.2, 101.7, 101.5, 61.1, 14.0, 13.7.
HRMS: calcd for $C_{14}H_{12}FN_2O_3$, (MH^+) 275.0832, found 275.0824.
Spectral data for ethyl 3-(2-chlorophenyl)-5-methylisoxazole-4-carboxylate (**4**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.31 (m, 4H), 4.15 (q, J = 7.0 Hz, 2H), 2.77 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 161.6, 160.8, 134.1, 130.9, 130.7, 129.3, 128.8, 126.5, 109.9, 60.6, 13.6, 13.1.
Spectral data for ethyl 3-(3-chlorophenyl)-5-methylisoxazole-4-carboxylate (**5**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (t, J = 1.6 Hz, 1H), 7.53 (dt, J = 7.7, 1.3 Hz, 1H), 7.48–7.43 (m, 1H), 7.42–7.35 (m, 1H), 4.26 (q, J = 7.3 Hz, 2H), 2.75 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 161.7, 161.3, 133.8, 130.2, 129.7, 129.6, 129.2, 127.6, 108.4, 60.8, 13.9, 13.5.
Spectral data for ethyl 3-(2,5-dimethoxyphenyl)-5-methylisoxazole-4-carboxylate (**7**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.94 (m, 2H), 6.90–6.81 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 2.71 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 162.1, 160.0, 153.3, 151.7, 118.8, 116.3, 115.6, 111.8, 110.2, 60.3, 55.9, 55.8, 13.8, 12.9.
HRMS: calcd for $C_{15}H_{18}NO_5$, (MH^+) 292.1185, found 292.1174.
Spectral data for ethyl 3-(2-chloro-4-fluorophenyl)-5-methylisoxazole-4-carboxylate (**8**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.5, 6.0 Hz, 1H), 7.24 (dd, J = 8.5, 2.5 Hz, 1H), 7.08 (td, J = 8.3, 2.5 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.77 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 164.5, 162.0, 161.5, 160.1, 135.3, 135.2, 132.2, 132.1, 125.0 (d, J = 3.9 Hz, 1C), 117.1, 116.9, 114.0, 113.8, 109.8, 60.7, 13.7, 13.2.
HRMS: calcd for $C_{13}H_{12}ClFNO_3$, (MH^+) 284.0490, found 284.0481.
Spectral data for ethyl 3-(3-bromopyridin-2-yl)-5-methylisoxazole-4-carboxylate (**9**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 4.8, 1.5 Hz, 1H), 8.05–7.96 (m, 1H), 7.31 (ddd, J = 8.0, 4.8, 1.5 Hz, 1H), 4.18–4.08 (m, 2H), 2.78 (d, J = 1.5 Hz, 3H), 1.05 (td, J = 7.1, 1.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 161.0, 161.0, 148.9, 147.6, 140.2, 125.2, 121.8, 109.4, 60.6, 13.6, 13.0. HRMS: calcd for $C_{12}H_{12}BrN_2O_3$, (MH^+) 311.0031, found 311.0020.
Spectral data for ethyl 5-methyl-3-(1-phenylethyl)isoxazole-4-carboxylate (**11**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 4.3 Hz, 4H), 7.23–7.17 (m, 1H), 4.68 (q, J = 7.3 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H), 2.64 (s, 3H), 1.68 (d, J = 7.3 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 165.6, 162.0, 143.2, 128.3 (s, 2C), 127.6 (s, 2C), 126.5, 108.0, 60.4, 37.6, 20.9, 14.1, 13.4.
Spectral data for methyl 3-(2-methoxyphenyl)-5-methylisoxazole-4-carboxylate (**12**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.39 (m, 2H), 7.05 (td, J = 7.5, 0.9 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 162.8, 160.1, 157.4, 131.5, 130.2, 120.5, 117.6, 110.8, 110.1, 55.4, 51.6, 13.0.
Spectral data for methyl 3-(2-methoxyphenyl)-4-methylisoxazole-5-carboxylate (**13**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.44 (m, 1H), 7.39 (dd, J = 7.5, 1.8 Hz, 1H), 7.12–6.99 (m, 2H), 4.00 (s, 3H), 3.84 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 158.4, 157.3, 154.7, 131.6, 131.3, 122.6, 120.8, 117.3, 111.1, 55.5, 52.4, 8.6.
Spectral data for 1-(3-(2-methoxyphenyl)-5-phenylisoxazol-4-yl)ethanone (**14**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.8, 1.8 Hz, 2H), 7.64 (dd, J = 7.5, 1.8 Hz, 1H), 7.56–7.48 (m, 4H), 7.13 (td, J = 7.5, 1.0 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 194.9, 169.6, 159.7, 156.7, 132.0, 131.2, 130.5, 128.7 (s, 2C), 128.6 (s, 2C), 126.9, 121.2, 118.0, 117.6, 111.0, 55.1, 29.9.