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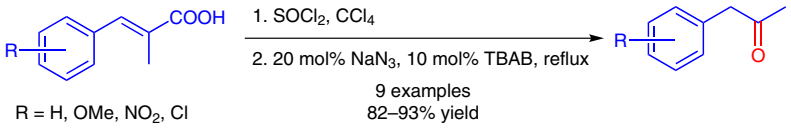
A Convenient and Efficient One-Pot Synthesis of Arylacetones from (*E*)-3-Aryl-2-methylacrylic Acids by Curtius Rearrangement

Xin He
Chong Cao
Jingwei Liang
Xinyang Li
Tingjian Zhang
Fanhao Meng*

Department of Medicinal Chemistry, School of Pharmacy, China Medical University, No. 77 Puhe Road, Shenyang, Liaoning, 110122, P. R. of China
fhmeng@cmu.edu.cn



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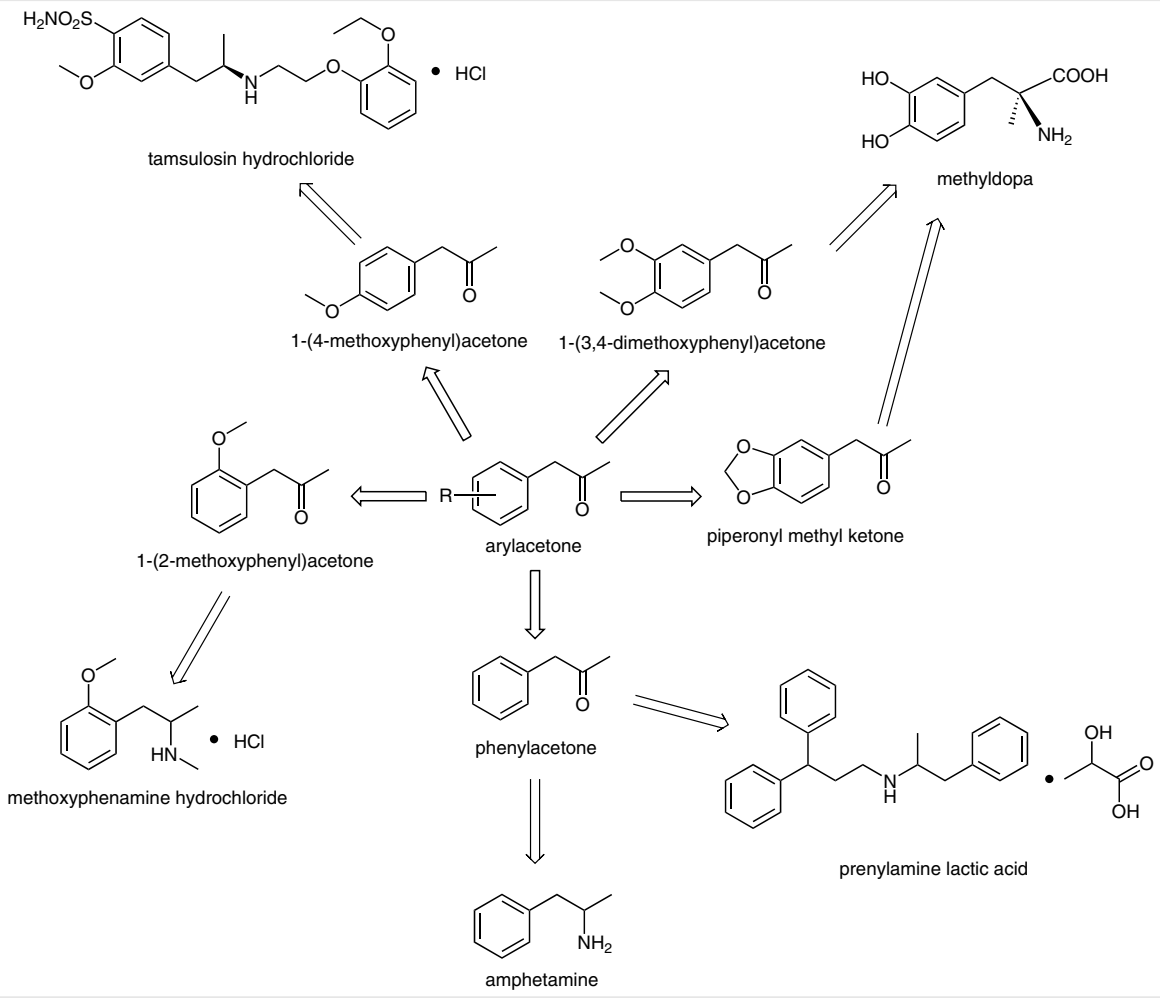
Abstract A convenient and efficient method was developed for the synthesis of arylacetones from (*E*)-3-aryl-2-methylacrylic acids through a Curtius rearrangement. The Curtius rearrangement of (*E*)-3-aryl-2-methylacryloyl azides and subsequent hydrolysis proceeded at mild temperatures in a two-phase medium of carbon tetrachloride and water containing a catalytic amount of tetrabutylammonium bromide to give the corresponding derivatives in 82–93% yield.

Key words arylacetones, Curtius rearrangement, methylarylacrylic acids, phase-transfer catalysis, acryloyl azides

Arylacetones are important synthetic building blocks with a wide range of applications in the fine chemical, agrochemical, and pharmaceutical industries.[1–3] For instance, 1-(4-methoxyphenyl)acetone is an important intermediate for the synthesis of tamsulosin hydrochloride, a drug for the treatment of benign prostatic hyperplasia; 1-(3,4-dimethoxyphenyl)acetone and 1-(3,4-methylenedioxyphenyl)acetone are used as raw materials, critical for the preparation of methyldopa; and 1-(2-methoxyphenyl)acetone is a key intermediate for the preparation of methoxyphenamine hydrochloride, an antiasthmatic drug (Scheme 1). Amphetamine and prenylamine lactic acid, for the treatment of brain dysfunction in children and angina, respectively, are both synthesized by using 1-phenylacetone as a starting material.

Because of their synthetic value, a number of methods have been developed for the preparation of arylacetones.[4] One interesting synthetic route brought to our attention is that using benzyl chloride derivatives as starting materials to prepare benzylzinc(II) chloride derivatives that undergo nucleophilic addition with acetic anhydride to give arylacetones (Scheme 2). However, two aspects of this synthetic route need to be improved. First, obtaining the benzylzinc(II) chloride derivatives is difficult because of the low reactivity of zinc under the experimental conditions, and the consequent need for anhydrous conditions. Secondly, the precise reaction temperature is difficult to control. On increasing the reaction temperature, an alcoholic byproduct can be formed in the reaction system. A similar synthetic strategy involving the nucleophilic addition of a benzylmagnesium chloride with acetonitrile, followed by hydrolysis, gives the corresponding phenylacetone in a good yield (Scheme 2). Unlike benzylzinc(II) chlorides, which are difficult to obtain because of the relative chemical inactivity of zinc, nucleophilic benzylmagnesium chlorides can be easily prepared and show a high reaction potential. Moreover, after nucleophilic addition of the benzylmagnesium chloride to acetonitrile, the intermediate imine is relatively stable and does not react with the benzylmagnesium chloride to form byproducts. However, it was found to be difficult to avoid the formation of a dimer through the alkylation of the benzylmagnesium chloride with the benzyl chloride during the preparation of the benzylmagnesium chloride (Scheme 2).

Inspired by the reaction mechanism of this method, we designed and developed a novel method for the preparation of arylacetones by using inexpensive commercially available compounds to form imines, instead of using Grignard reagents, eventually giving the target compounds through hydrolysis. We hypothesized that the carboxylic acid group directly connected to the unsaturated double bond in the aliphatic hydrocarbon moiety of (*E*)-3-aryl-2-methylacrylic acids might be used to introduce the skeleton of an imide. If the carboxylic acid group was replaced by an amine group, 3-aryl-2-methylacrylic acids might be converted into the corresponding 1-arylprop-1-en-2-amines. These could then be converted into 1-arylpropan-2-imines by tautomerization. On this basis of this hypothesis, we developed a novel synthetic route for the synthesis of arylacetones by convert-



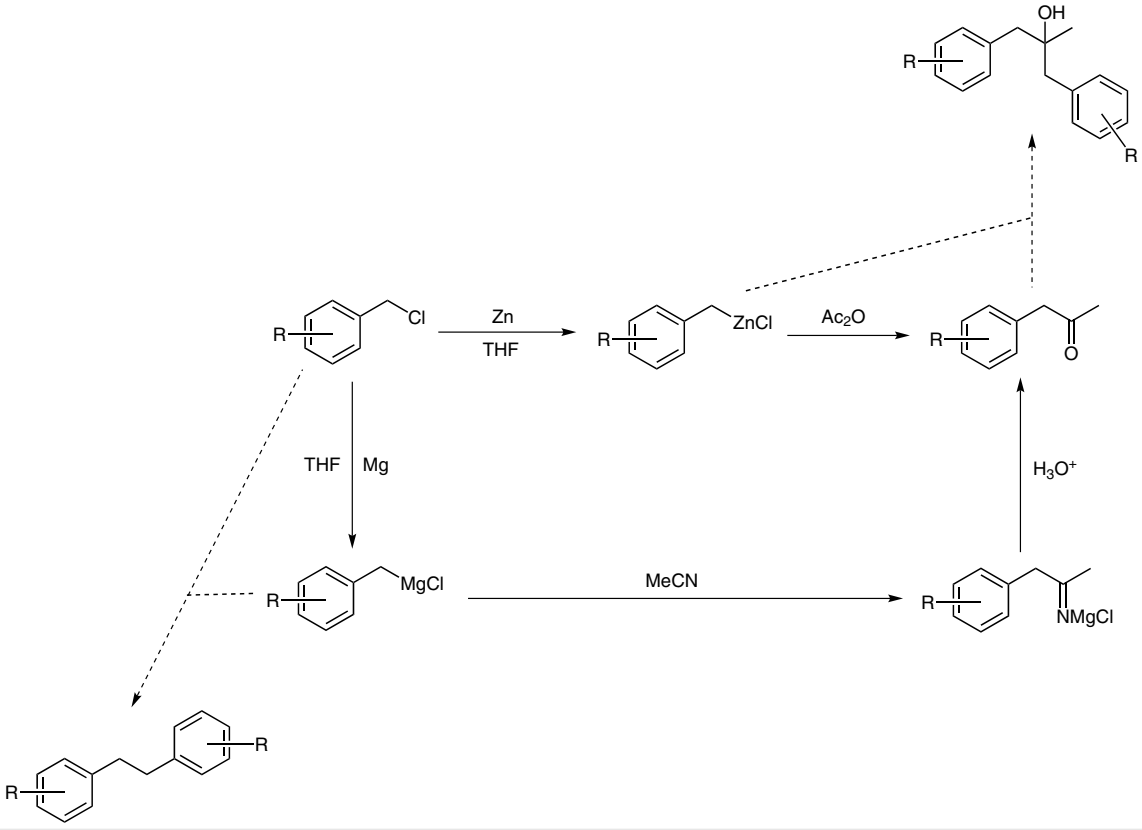
Scheme 1 1-Arylacetones as key intermediates for drugs

ing the carboxylic acid group of (*E*)-3-aryl-2-methylacrylic acids into an amino group through a Curtius rearrangement (Scheme 3).

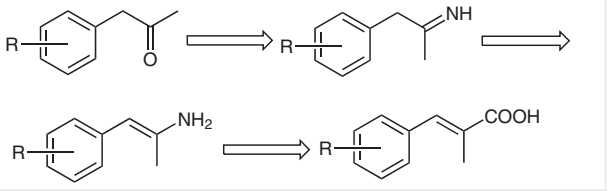
The Curtius rearrangement is an effective reaction for the preparation of amino derivatives, and a number of methods have been developed to synthesize acyl azides from carboxylic acid derivatives.[5] Acyl azides are initially converted into isocyanates by rearrangement, and the isocyanates subsequently react with various compounds to form amine derivatives with one fewer carbon atom. Although the Curtius rearrangement has been applied in a number of organic transformations, such as the syntheses of 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide,[6] tyramine,[7] sulfonylureas,[8] oseltamivir (Tamiflu),[9] and alkyl *N*-(1-cyclohex-3-enyl)carbamates,[10] to the best of our knowledge, its application in the synthesis of arylacetones has not been reported.

As the Curtius rearrangement is one of our interests, and because (*E*)-3-aryl-2-methylacrylic acids are widely available,[11,12] we developed a convenient and effective protocol for the synthesis of arylacetones by a one-pot two-step reaction of (*E*)-3-aryl-2-methylacryloyl chlorides with sodium azide, followed by hydrolysis in aqueous medium.[13]

In our previous work, we reported the preparation of arylacetones from (*E*)-3-aryl-2-methylacrylic acids through diazotization of the corresponding (*E*)-3-aryl-2-methylacryloyl hydrazines, Curtius rearrangement, and hydrolysis.[14] In this synthetic route, the formation of (*E*)-3-aryl-2-methylacryloyl hydrazines from (*E*)-3-aryl-2-methylacrylic acids requires an additional esterification step before hydrazinolysis, making the method more complicated and less practical.



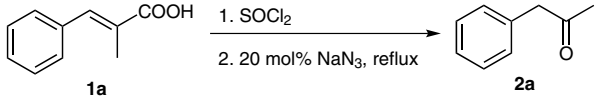
Scheme 2 Two routes to arylacetones by nucleophilic addition reactions



Scheme 3 Proposed route for converting (*E*)-3-aryl-2-methylacrylic acids into arylacetones

Acyl azides can also be obtained in satisfactory yields by acylation of sodium azide with acyl chlorides.[5d–g] (*E*)-3-Aryl-2-methylacryloyl chlorides are relatively stable in water at low temperatures, so we envisaged that aqueous sodium azide might be used as a source of azide to react with (*E*)-3-aryl-2-methylacryloyl chlorides to generate (*E*)-3-aryl-2-methylacryloyl azides that would undergo subsequent Curtius rearrangement and hydrolysis in one pot.

As a typical example, the synthesis of (*E*)-2-methyl-3-phenylacryloyl chloride was initiated by adding thionyl chloride (1.01 equiv) to a (*E*)-2-methyl-3-phenylacrylic acid solution in various reaction media at 35 °C for 30 minutes. This was followed by the direct addition of 20% aqueous sodium azide (1.01 equiv) directly to the above system at room temperature under vigorous stirring for another 30 minutes. The mixture was then refluxed for the specified time (Scheme 4). To obtain a better yield, key factors in the reaction were optimized by monitoring the yield of the products (Table 1). Three reaction media (dichloromethane, chloroform, and carbon tetrachloride) and two reaction times (3 and 1.5 hours) were tested during the optimization. Dichloromethane emerged as the worst solvent, giving only 11% yield of 1-phenylacetone (Table 1, entry 1). Adding tetrabutylammonium bromide (TBAB) as a surfactant doubled the yield (entry 2). On changing the reaction medium to chloroform or carbon tetrachloride containing a catalytic amount of TBAB, yields of 62% and 93% were obtained after 1.5 hours (entries 3 and 4).



Scheme 4 Preparation of 1-phenylacetone

Table 1 Optimization of the Reaction Conditions

Entry	Reaction medium	Reflux time (h)	Yield (%)
1	CH_2Cl_2	3	11
2	CH_2Cl_2 + TBAB (10 mol%)	3	25
3	$CHCl_3$ + TBAB (10 mol%)	1.5	62
4	CCl_4 + TBAB (10 mol%)	1.5	93
5	DCE + TBAB (10 mol%)	1.5	90

The best yield (93%) of 1-phenylacetone (**2a**) was obtained with carbon tetrachloride as the reaction medium (entry 4); this might be due to the high boiling point of this solvent, as the Curtius rearrangement requires a relatively high temperature. The use of refluxing carbon tetrachloride as a reaction medium is sufficient to provide the activation energy necessary for the rearrangement of acyl azides, leading to completion of the rearrangement reaction, thereby increasing the reaction rate and yield. The reaction temperature is therefore a key factor in determining the reaction rate and the product yield. To confirm this finding, we used DCE as a medium, and we found that with the same reaction time, a similar yield (90%) of 1-phenylacetone (**2a**) was obtained (entry 5).

With the optimized conditions in hand, we investigated the synthesis of a group of 1-arylacetones from various (*E*)-3-aryl-2-methylacrylic acids as starting materials (Table 2).[15] The reactions proceeded smoothly in all cases, giving the corresponding products **2a–i** in yields of 82–93% (Table 2, entries 1–9). No distinct substituent effect of the (*E*)-3-aryl-2-methylacrylic acid substrates was observed, and substrates with electron-donating or electron-withdrawing groups gave the corresponding products in good yields and in similar reaction times (1.5–2 h). This, therefore, is a unique route for the preparation of several of 1-arylacetones.

In conclusion, a convenient and efficient method was developed for the preparation of arylacetones from (*E*)-3-aryl-2-methylacrylic acids. The protocol permits both the rearrangement of the (*E*)-3-aryl-2-methylacryloyl azides and the subsequent hydrolysis to be carried out in one pot under mild conditions. A series of 1-arylacetone derivatives were synthesized successfully in yields of 82–93%. Further optimization to broaden the scope and applications of this method are currently underway, and will be reported in due course.

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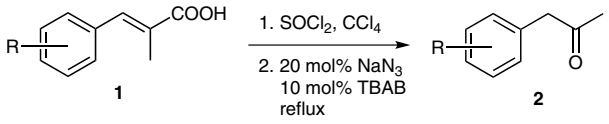
Table 2 Synthesis of 1-Arylacetones **2a–i**



Entry	Product	R	Time[a] (h)	Yield (%)
1	**2a**	H	1.5	93
2	**2b**	3,4,5-$(MeO)_3$	1.5	86
3	**2c**	3,4-$(MeO)_2$	1.5	82
4	**2d**	4-MeO	1.5	87
5	**2e**	2-MeO	1.5	89
6	**2f**	3-O_2N	2	85
7	**2g**	4-O_2N	2	88
8	**2h**	3-Cl	1.5	85
9	**2i**	4-Cl	1.5	83

[a] Reflux time in step 2.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588905.

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(12) The various (*E*)-3-aryl-2-methylacrylic acids were obtained from commercial sources.

(13) **1-Arylacetones 2a–i; General Procedure**
A well-stirred mixture of the appropriate (*E*)-3-aryl-2-methylacrylic acid **1** (30 mmol) and $SOCl_2$, (30.3 mmol) in CCl_4 (50 mL) was heated at 35 °C for 30 min. 20% aq NaN_3 (30.3 mmol) and TBAB (0.97 g, 10 mol%) were added at r.t., and the mixture was stirred for another 30 min, then heated to the reflux temperature. When the reaction was complete (1.5–2 h; Table 2), the aqueous layer was separated and extracted with CCl_4 (3 × 20 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc–PE). All products were identified by ^1H and ^{13}C NMR and MS spectral analysis.

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(15) **1-Phenylacetone (2a)**
Colorless oil; yield: 3.75 g (93%). ^1H NMR (600 MHz, DMSO-d_6): δ = 7.29–7.34 (m, 2 H), 7.22–7.26 (m, 1 H), 7.18–7.21 (m, 2 H), 3.75 (s, 2 H), 2.12 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 206.2, 135.3, 130.0, 128.7, 126.9, 50.0, 29.7. GC-MS (EI): *m/z* = 134.2 [M$^+$].

1-(3,4,5-Trimethoxyphenyl)acetone(2b)
Faintly yellow solid; yield: 5.78 g (86%), mp 88–91 °C. ^1H NMR (600 MHz, DMSO-d_6): δ = 6.49 (s, 2 H), 3.74 (s, 6 H), 3.66 (s, 2 H), 3.63 (s, 3 H), 2.11 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 206.4, 153.1, 136.6, 130.9, 107.2, 60.3, 56.1, 50.3, 29.7. GC-MS (EI): *m/z* = 224.2 [M$^+$].

1-(3,4-Dimethoxyphenyl)acetone (2c)
Yellow oil; yield: 4.78 g (82%). ^1H NMR (600 MHz, DMSO-d_6): δ = 6.87 (d, *J* = 8.1 Hz, 1 H), 6.78 (d, *J* = 1.9 Hz, 1 H), 6.70 (dd, *J* = 8.1, 2.1 Hz, 1 H), 3.72 (s, 6 H), 3.64 (s, 2 H), 2.09 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 206.7, 149.0, 148.0, 127.7, 121.9, 113.7, 112.2, 55.8, 55.8, 49.7, 29.5. GC-MS (EI): *m/z* = 194.2 [M$^+$].

1-(4-Methoxyphenyl)acetone (2d)
Yellow oil; yield: 4.29 g (87%). ^1H NMR (600 MHz, DMSO-d_6): δ = 7.08–7.11 (m, 2 H), 6.84–6.89 (m, 2 H), 3.72 (s, 3 H), 3.66 (s, 2 H), 2.08 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 206.7, 158.4, 130.9, 127.2, 114.1, 55.3, 49.2, 29.6. GC-MS (EI): *m/z* = 164.2 [M$^+$].

1-(2-Methoxyphenyl)acetone (2e)
Yellow oil; yield: 4.39 g (89%). ^1H NMR (600 MHz, DMSO-d_6): δ = 7.19–7.26 (m, 1 H), 7.12 (d, *J* = 7.3 Hz, 1 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.88 (t, *J* = 7.3 Hz, 1 H), 3.73 (s, 3 H), 3.64 (s, 2 H), 2.07 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 206.2, 157.5, 131.5, 128.6, 124.2, 120.6, 111.0, 55.7, 45.0, 29.7. GC-MS (EI): *m/z* = 164.2 [M$^+$].

1-(3-Nitrophenyl)acetone (2f)
Yellow solid; yield: 4.57 g (85%); mp 64–66 °C. ^1H NMR (600 MHz, DMSO-d_6): δ = 8.04–8.11 (m, 2 H), 7.54–7.65 (m, 2 H), 4.00 (s, 2 H), 2.19 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 205.5, 148.0, 137.6, 137.1, 129.8, 124.8, 121.8, 48.7, 30.1. GC-MS (EI): *m/z* = 179.2 [M$^+$].

1-(4-Nitrophenyl)acetone (2g)
Faintly yellow solid; yield: 4.73 g (88%); mp 203–206 °C. ^1H NMR (600 MHz, DMSO-d_6): δ = 8.12–8.21 (m, 2 H), 7.37–7.51 (m, 2 H), 3.99 (s, 2 H), 2.19 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 205.2, 146.7, 143.5, 131.5, 123.5, 49.2, 30.2. GC-MS (EI): *m/z* = 179.2 [M$^+$].

1-(3-Chlorophenyl)acetone (2h)
Yellow oil; yield: 4.30 g (85%). ^1H NMR (600 MHz, DMSO-d_6): δ = 7.32 (t, *J* = 7.7 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 1 H), 7.26 (s, 1 H), 7.13 (d, *J* = 7.3 Hz, 1 H), 3.80 (s, 2 H), 2.14 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 205.7, 137.8, 133.2, 130.3, 129.9, 128.8, 126.8, 49.1, 30.0. GC-MS (EI): *m/z* = 168.6 [M+].

1-(4-Chlorophenyl)acetone (2i)
Yellow oil; yield: 4.20 g (83%). ^1H NMR (600 MHz, DMSO-d_6): δ = 7.32–7.39 (m, 2 H), 7.14–7.24 (m, 2 H), 3.78 (s, 2 H), 2.13 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 205.9, 134.3, 131.9, 131.7, 128.5, 49.0, 29.9. GC-MS (EI): *m/z* = 168.6 [M$^+$].