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Oxidative Cleavage of the Carbon–Carbon σ-Bond Using Reusable Copper on Iron

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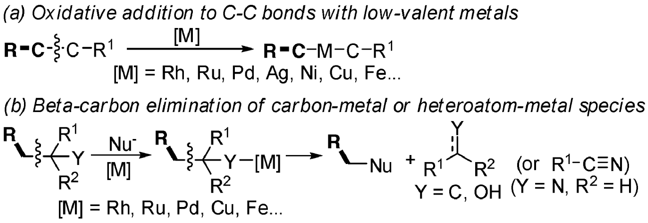
Abstract: An efficient and resuble copper on iron catalyst has been prepared for the cleavage of the carbon-carbon σ-bond in α-aminocarbonyl compounds leading to the corresponding formylamides and acids with a maximal TON of up to 51,000. It is noteworthy that the copper on iron catalyst can be easily separated from the reaction mixture, and retains its activity after several reuses.

Keywords: α-aminocarbonyl compounds; copper; formylamides; iron; oxidative cleavage; reusable catalysts

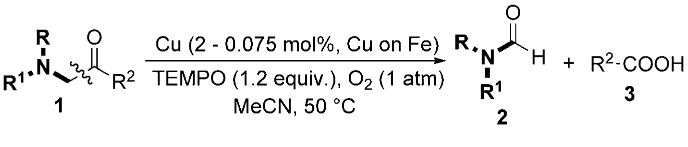
Transition metal-catalyzed cleavage of the carbon-carbon bond,[1] particularly the inert carbon-carbon σ-bond, is one of the most challenging tasks in organic chemistry. Until now, numerous unique and useful carbon-carbon bond cleavage procedures have been developed using stoichiometric or catalytic amounts of transition metals, such as rhodium,[2] ruthenium,[3] gold,[4] palladium,[5] silver,[6] nickel,[7] copper[8] or iron[9] catalysts. Among these procedures, two general routes to the carbon-carbon σ-bond cleavage include (i) oxidative addition to the C–C bonds with low-valent metals through an insertion process,[7,10] which often employs the strained ring as the reaction partner, and (ii) β-carbon elimination of the carbon-metal species (M–C–C–C)[3b,11] or heteroatom-metal species (M–Y–C–C, Y = O, N) (Scheme 1).[2i,5a–d,12]

However, all these procedures are restricted in both the cost and loading of the catalysts. To the best of our knowledge, examples on the use of lower-loading and reusable catalysts for the purpose of carbon-carbon σ-bond cleavage have not been described. Here, we report a new, reusable copper on iron heterogeneous catalyst for cleaving the carbon-carbon σ-bond in α-aminocarbonyl compounds with the aid of TEMPO and O_2, providing the corresponding formylamides and acids in moderate to good yields (Scheme 2).[13] It is noteworthy that the carbon-carbon single bond cleavage can be carried out under conditions of relatively lower loading of Cu with a maximal TON (turnover number) of up to 51,000.

Our investigation began with the reaction of 2-[methyl(phenyl)amino]-1-phenylethanone (**1a**) in MeCN at 50 °C for 12 h under an O_2 atmosphere; however, the reaction did not take place (entry 1 in Table 1). Interestingly, the reaction proceeded smoothly when both 2 mol% Cu (Cu on Fe) and O_2 were added, providing the corresponding *N*-methyl-*N*-phenylformamide (**2a**) in 61% yield along with a

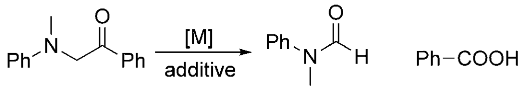


Scheme 1. Two routes to the carbon-carbon σ-bond cleavage.



Scheme 2. Cu-catalyzed oxidative carbon-carbon σ-bond cleavage.

Table 1. Screening for the reaction conditions.[a]



Entry	[M] (weight%)	Additive	Solvent	Yield [%][b]	
				2a	3a
1	–	–	MeCN	0	0
2	Cu/Fe	–	MeCN	61	50
3	Cu/Fe	TEMPO	MeCN	85	65
4	–	TEMPO	MeCN	9	trace
5	Cu (98.5674%)	TEMPO	MeCN	69	ND
6	Cu (99.5%)	TEMPO	MeCN	76	ND
7	Cu (99.999%)	TEMPO	MeCN	82	65
8	Fe (88.2667%)	TEMPO	MeCN	41	ND
9	Fe (99.5%)	TEMPO	MeCN	18	ND
10	Fe (99.998%)	TEMPO	MeCN	10	ND
11	Cu on Fe	TEMPO	CH_2Cl_2	76	ND
12	Cu on Fe	TEMPO	THF	68	ND
13	Cu on Fe	TEMPO	DMF	60	ND
14	Cu on Fe	TEMPO	DMSO	62	ND
15[c]	Cu on Fe	TEMPO	MeCN	63	ND
16[d]	Cu on Fe	TEMPO	MeCN	22	ND
17[e]	Cu on Fe	TEMPO	MeCN	trace	ND
18[f]	Cu on Fe	TEMPO	MeCN	70	ND
19[g]	Cu on Fe	TEMPO	MeCN	80	62
20[h]	Cu on Fe	TEMPO	MeCN	86	71
21[i]	Cu on Fe	TEMPO	MeCN	38	27

[a] *Reaction conditions:* **1a** (0.2 mmol), additive (1.2 equiv.), [M] (2 mol%), O_2 (1 atm) and solvent (2 mL) at 50 °C for 12 h. Cu/Fe (wt%): 37.5% Cu and 31.3% Fe. ND = not determined.

[b] Yield of isolated products.

[c] Air (1 atm) instead of O_2.

[d] Under the argon atmosphere.

[e] At room temperature.

[f] At 80 °C.

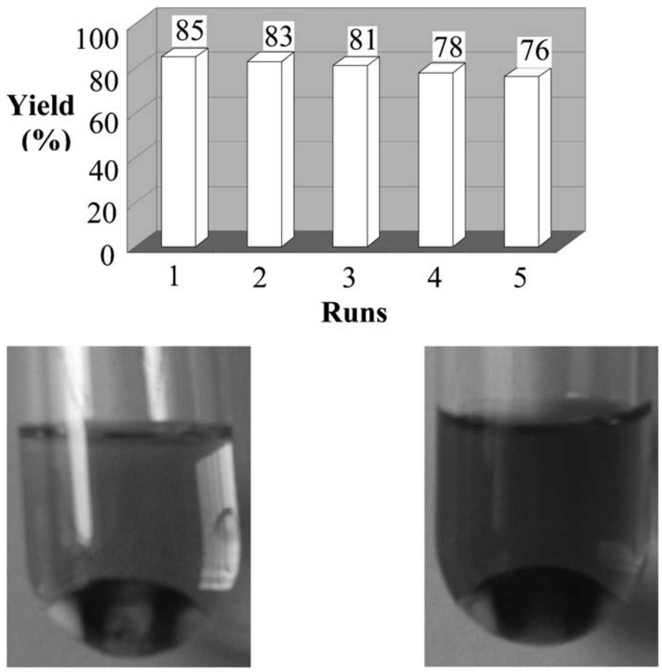
[g] At 100 °C.

[h] **1a** (10 mmol).

[i] **1a** (10 mmol) and Cu (0.075 mol%, Cu on Fe) for 12 h, and the TON was 51000.

50% yield of benzoic acid (**3a**) (entry 2). We were pleased to find that TEMPO could facilitate the reaction: the yield was enhanced to 85% together with benzoic acid (**3a**) in 65% yield in the presence of 1.2 equivalents of TEMPO (entry 3). To our surprise, the reaction could run in 9% yield of **2a** after 12 h in the presence of TEMPO alone (entry 4). The reason may be that there is some copper leftover in TEMPO as determined by ICP-MS analysis.[14] Subsequently, the catalytic activities of Cu or Fe powders were investigated to better understand of the reaction. Interestingly, the results demonstrated that the catalytic activities of Cu or Fe powders are affected by their purity (entries 5–10). While commercially available common Cu powders (purity: wt% Cu = 98.5674%) displayed lower activity leading to 69% yield of **2a** (entry 5), the yield was enhanced to 76% using a purity of 99.5 wt% for Cu and to 82% yield with a purity of 99.999 wt% Cu (entries 6 and 7). On the contrary, the catalytic activities of Fe powders were decreased with increasing purity (entries 8–10). Commercially available common Fe powders (purity: wt% Fe = 88.2667%) afforded product **2a** in 41% yield (entry 8), whereas use of 99.5% purity Fe lowered the yield of **2a** to 18% and to 10% yield when using 99.998% purity Fe (entries 9 and 10). These observations suggest that Cu is the real catalyst, and Fe may play a part as ligand to improve the reaction to some extent.

The screening results demonstrated that the solvent effect has some influence on the reaction, other solvents, such as CH_2Cl_2, THF, DMF and DMSO, were effective for the reaction, but they were inferior to MeCN (entries 11–14). It is noteworthy that oxygen is necessary for the reaction: the yield of **2a** was reduced to 63% in air and to 22% in argon (entries 15 and 16). From a reaction temperature screen, it turned out that the reaction at 50 °C gave the best results (entries 3 and 17–19). Notably, the reaction conditions are compatible with a large scale: 10 mmol of 2-[methyl(phenyl)amino]-1-phenylethanone (**1a**) were treated with 2 mol% Cu on Fe, TEMPO and O_2 and recated smoothly to furnish an 86% yield of **2a** and a 71% yield **3a** (entry 20). To our delight, the reaction could be carried out at a relatively lower loading of Cu: 0.075 mol% Cu (Cu on Fe) which furnished the



Before the reaction After the reaction

Figure 1. Reuse of the Cu on Fe catalyst during the reaction of **1a**: (*left*) before the reaction, (*right*) after the reaction. The Cu on Fe catalyst was absorbed on the stirred bar.

desired product **2a** in 38% yield in 12 h along with product **3a** in 30% yield (TON = 51,000, entry 21).

As shown in Figure 1, the recycling of the copper on iron catalyst during the reaction of substrate **1a** was tested using an external magnetic field. The experiments indicated that the copper on iron catalyst could be reused at least 5 times without losing catalytic activity. After initial experimentation, the reaction mixture was removed, the catalyst was washed, dried, and subjected to a second run of the oxidative cleavage by charging with the same substrate **1a**, oxidizing reagents and solvent for 12 h. Gratifyingly, five runs were almost consistent in yields, suggesting that the activity of the Cu on Fe catalyst was not obviously decreased during the recycling processes. However, the loss of some Cu species during the reuse experiments resulted in a slight reduction of the yields.

The scope of α-aminocarbonyl compounds was then explored in the presence of Cu on Fe, TEMPO and O_2, and the results are summarized in Table 2. The results demonstrate that numerous substituents, such as MeO, Me, Ph, Cl or NO_2, on aryl ring of the 1-arylethanone moiety were perfectly tolerated under the standard conditions (entries 1–10). Substrate **1b** with a methoxy group, for instance, was treated with Cu on Fe, TEMPO and O_2 to smoothly afford the de-

Table 2. The carbon-carbon bond cleavage reactions of α-aminocarbonyl compounds (**1**) using the copper on iron catalyst.[a]

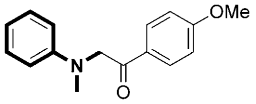
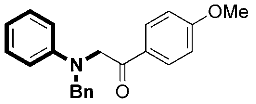
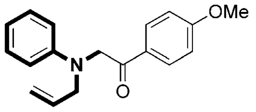
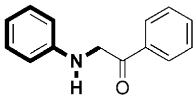
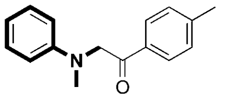
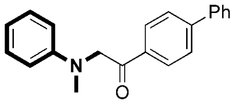
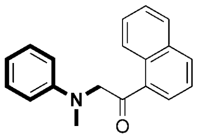
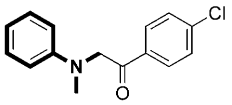
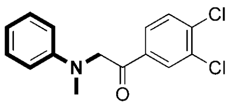
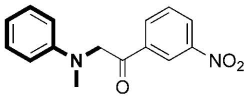
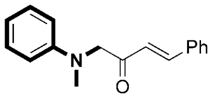
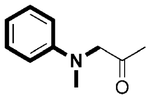
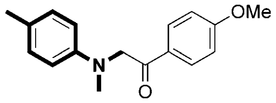
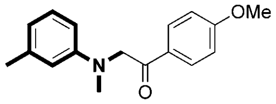
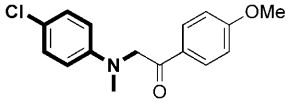
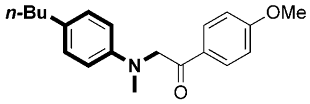
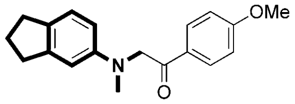
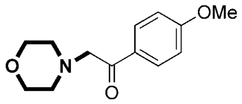
Entry	α-Aminocarbonyl (**1**)		Time [h]	Yield [%][b] **2**	**3**
1		(**1b**)	10	78 (**2a**)	62 (**3b**)
2		(**1c**)	8	75 (**2c**)	60 (**3b**)
3		(**1d**)	8	72 (**2d**)	64 (**3b**)
4[c]		(**1e**)	12	40 (**2e**)	55 (**3b**)
5		(**1f**)	12	81 (**2a**)	66 (**3f**)
6		(**1g**)	9	63 (**2a**)	43 (**3g**)
7		(**1h**)	8	83 (**2a**)	50 (**3h**)
8		(**1i**)	12	69 (**2a**)	61 (**3i**)
9		(**1j**)	12	71 (**2a**)	69 (**3j**)
10		(**1k**)	16	58 (**2a**)	45 (**3k**)

Table 2. (Continued)

Entry	α-Aminocarbonyl (**1**)		Time [h]	Yield [%][b]	
				2	**3**
11		(**1l**)	17	68 (**2a**)	59 (**3l**)
12[d]		(**1m**)	30	63 (**2a**)	60 (**3m**)
13		(**1n**)	13	85 (**2n**)	72 (**3b**)
14		(**1o**)	13	68 (**2o**)	50 (**3b**)
15		(**1p**)	13	71 (**2p**)	58 (**3b**)
16		(**1q**)	9	65 (**2q**)	55 (**3b**)
17		(**1r**)	12	71 (**2r**)	57 (**3b**)
18		(**1s**)	38	50 (**2s**)	73 (**3b**)

[a] *Reaction conditions:* **1a** (0.2 mmol), Cu (2 mol%, Cu on Fe), TEMPO (1.2 equiv.), O_2 (1 atm) and MeCN (2 mL) at 50 °C.

[b] Yield of isolated product.

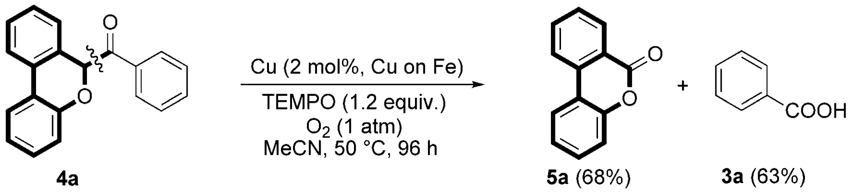
[c] Some unidentified by-products were observed.

[d] GC yield of **3m** using nitrobenzene as the internal standard.

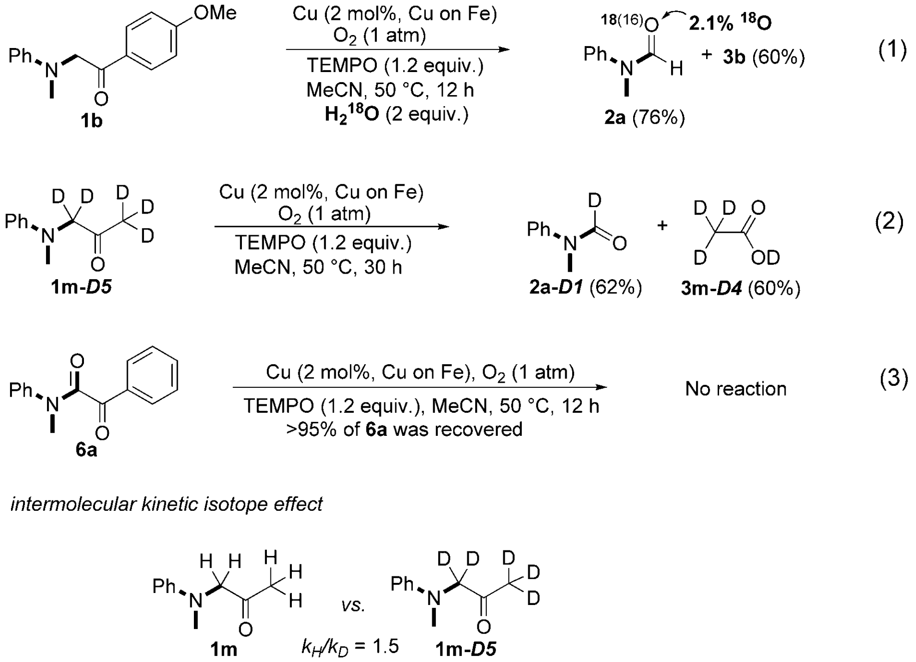
sired products **2a** and **3b** in 78% and 62% yields, respectively (entry 1). We were delighted to discover that the analogous ketones **1c** and **1d** with the *N*-methyl group replaced by a benzyl group or an allyl group were compatible with the standard reaction conditions (entries 2 and 3). Notably, 1-phenyl-2-(phenylamino)ethanone (**1e**), a secondary amine, was also suitable for the cleavage reaction (entry 4). Substrates **1i** and **1j** bearing chloro groups successfully underwent the reaction to furnish the corresponding products in good yields (entries 8 and 9). Moderate yields were still achieved from NO_2-substituted substrate **1k** (entry 10). Gratifyingly, α-amino enone **1l** could be cleaved by Cu on Fe, TEMPO and O_2 leading to 68% yield of *N*-methyl-*N*-phenylformamide (**2a**) and 59% yield of cinnamic acid (**3l**) (entry 11). It is noteworthy that the latter, cinnamic acid (**3l**), is widely used in flavors and fragrances, food additives, and the pharmaceutical industry. Interestingly, the standard conditions were also compatible with aliphatic ketone **1m** (entry 12).

Subsequently, the substitutents on the *N*-aryl ring were investigated (entries 13–17). The results showed that substrates **1n**–**1r**, having either alkyl or chloro groups, were successfully reacted with Cu on Fe, TEMPO and O_2 in good yields. For example, substrate **1r** with an *N*-2,3-dihydro-1*H*-inden-5-yl group provided the target products **2r** and **3b** in 71% and 57% yields, respectively (entry 17). It was interesting to observe that 1-(4-methoxyphenyl)-2-morpholinoethanone (**1s**) was effectively cleaved to the desired products under the standard conditions (entry 18).

As shown in Scheme 3, this present methodology was applied to the synthesis of 6*H*-benzo[*c*]chromen-6-one (**5a**), which displays great potential utilizations in organic synthesis and for the preparation of pharmaceuticals, such as estrogen receptor modulators.[15] In the presence of Cu on Fe, TEMPO and O_2, (6*H*-



Scheme 3. Application of this carbon-carbon bond cleavage reaction.



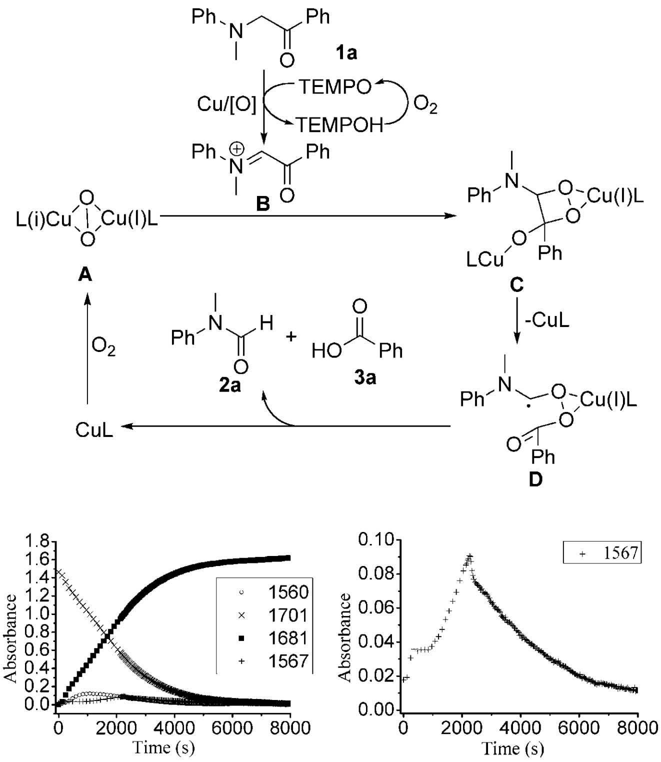
Scheme 4. Control experiments.

benzo[*c*]chromen-6-yl)(phenyl)methanone (**4a**) selectively underwent the cleavage reaction to afford the desired product **5a** in 68% yield along with benzoic acid (**3a**) in 63% yield.

To understand the mechanism, some control experiments were carried out (Scheme 4). The cleavage reaction of **1a** was tested in the presence of 2 equivalents of $H_2{}^{18}O$ under the standard conditions [Eq. (1)]. However, only a content of 2.1% of the ^{18}O-labeled product **2a** was determined by GC-MS analysis, suggesting the two new oxygen atoms in product **2a** are from O_2. The deuterium-labeled substrate **1m-*D5*** gave a monodeuterium-labeled product **2a-*D1*** [Eq. (2)]. The results showed that the reaction of *N*-methyl-2-oxo-*N*,2-diphenylacetamide (**6a**) did not take place in the presence of Cu on Fe, TEMPO and O_2 [Eq. (3)], which implies the reaction does not proceed *via* the dicarbonyl intermediate. The value of the intermolecular kinetic isotope effect ($k_H/k_D = 1.5$) implies that the C–H bond functionalization is the rate-limiting step.

The data of *in situ* FT-IR analysis indicated that substrate **1a** has two peaks: 1701 cm^{-1} (the C=O stretching vibration) and 1562 cm^{-1} (the N–H bending vibration). Interestingly, a new peak, 1567 cm^{-1}, is increasing and then decreasing over 1000–2000 s besides another peak at 1681 cm^{-1} (the C=O stretching vibration of **2a**) (Scheme 5). These results suggest that an imine intermediate is generated.[14,16]

Therefore, a possible mechanism as outlined in Scheme 5 was proposed.[13,16–18] Intermediate **A** is generated from the reaction of Cu with O_2,[13] followed by addition to the imine intermediate **B** to afford intermediate **C**.[17,18] The imine intermediate **B** is readily formed from substrate **1a** with the aid of Cu and oxidants, which is supported by *in situ* FT-IR analysis.[13,16] The cleavage of the C–C σ-bond and reductive elimination in intermediate **C** takes place leading to intermediate **D**. Intermediate **D** sequentially undergoes the O–O bond cleavage and reductive elimination to furnish the desired products and generate the CuL species.



Scheme 5. Possible mechanism and data of *in situ* FT-IR analysis during the reaction of **1a**.

In summary, we have prepared and successfully applied a copper on iron catalyst for the carbon-carbon σ-bond cleavage reaction of 2-substituted amino-1-phenylethanones. This catalyst allows a large-scale experiment (10 mol of **1a**. 2.25 g), and displays high catalytic activity with a maximal TON of up to 51,000. Importantly, the copper on iron catalyst can be easily separated from the reaction mixture, and retains its activity after several reuses. Work to extend the reaction and study the detailed mechanism is currently underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Cu on Fe Powders-Catalyzed Synthesis of Formamides 2 and Acids 3 in the Presence of O_2

To a Schlenk tube were added α-aminocarbonyl compound **1** (0.2 mmol), Cu (2 mol%, Cu on Fe), TEMPO (1.2 equiv.), and MeCN (2 mL). Then the tube was charged with O_2 (1 atm), and the mixture was stirred at 50 °C (oil bath temperature) for the indicated time until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction had finished, the reaction mixture was cooled to room temperature, diluted with diethyl ether, and washed with brine. The aqueous phase was re-extracted with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford the desired product.

***N*-Methyl-*N*-phenylformamide (2a):**[19] Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.41$ (s, 1H), 7.34 (t, $J = 8.0$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.10 (d, $J = 9.0$ Hz, 2H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.4$, 142.2, 129.6, 126.4, 122.4, 32.1; IR (KBr): $\nu = 1671$ cm^{-1}; LR-MS (EI 70 eV): m/z (%) = 135 (M^+, 68), 106 (100).

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