Aerial Oxidation of 2,2-Dibromo-1-Aryl and Heteroaryl Ethanones: A Facile Synthesis of Aryl and Heteroaryl α-Keto Amides

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Dedicated to Prof. H. Junjappa on the occasion of his 72nd birthday.

Abstract: The aerial oxidation of various 2,2-dibromo-1-aryl and heteroaryl ethanones to α-keto amides in the presence of air or oxygen and secondary amines are described. The reaction provides α-keto amides in moderate to good yields. The versatility of the reaction was established by synthesizing a series of α-keto amides by the reaction of dibromoethanones derived from aryl and heteroaryl ketones with cyclic and acyclic aliphatic secondary amines.

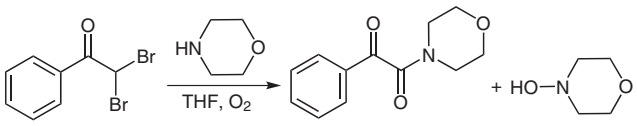
Key words: aerial oxidation, 2,2-dibromo-1-aryl and heteroaryl ethanone, α-keto amide, oxygen, secondary amine

The α-keto amides or α-oxoamides represent an important template that has attracted considerable interest because of its long history of applications in pharmaceutical industry.[1] They are the key skeletal framework of many biologically active compounds such as immunosuppressive drug FK506,[2] FKBP12,[3] rapamycine,[4] human cytosolic phospholipase A_2 (GIVA PLA_2) inhibitors,[5] androgen and estrogen receptors.[6] Consequently, they serve as useful synthetic intermediates. The α-keto amides are particularly important for the synthesis of sodium-channel blocker GW 356194,[7] nonimmunosuppressive compounds such as V-10367[8] and GPI-1046,[9] homoprotoberberines,[10] α-diones,[11] *cis*- and *trans*-isomers of β-lactam,[12] oxazolidin-4-ones,[13] and 5-HT_6 binding ligands.[14]

Although a number of methods are available for the synthesis of α-keto amides, a review of the literature confirms that the condensation of α-keto acid with amines by using dicyclohexylcarbodiimide and other activating groups are the most common method,[15] however, the complexities involved in the synthesis of α-keto acid makes this approach impractical. The carboxamide synthesis by palladium-catalyzed aminocarbonylation protocols utilizes carbon monoxide and results mixture of products.[16] The oxidative functionalization of *N*,*N*-(dialkyl)acylmethylamines with [{Fe(salen)}$_2$O] in the presence of 2-mercaptoethanol afforded the carboxamide in lower yields and utilizes inaccessible reagents.[17] The other methods reported in the literature[18–21] have several practical disadvantages like use of hazardous reagents, adiabatic reaction conditions, and lower yield. Therefore, development of a general and an efficient protocol for the synthesis of α-keto amide is highly desirable.

Herein we report an oxidative amidation protocol for the synthesis of α-keto amides by the reaction of 2,2-dibromo-1-aryl/heteroaryl ethanones with cyclic or acyclic secondary amine as well as amino acid ester in the presence of oxygen.

The synthesis of 1-phenyl-2-morpholin-1-yl-ethane-1,2-dione (**2a**) derived from dibromoacetophenone **1a** is outlined in Scheme 1. The required 2,2-dibromo-1-phenylethanone (**1a**) was prepared by the reaction of acetophenone with bromine in dioxane at room temperature[22] and was used for the oxidation reaction without further purification. The oxidative amidation was performed as described below. To a solution of dibromoacetophenone **1a** (1 g, 3.5 mmol, 1 equiv) in a 10-fold volume of THF was added morpholine (0.99 g, 14 mmol, 4 equiv) dropwise over a period of 30 minutes at 20–30 °C. The temperature of the reaction mixture was slowly raised to 40–50 °C under air and was maintained for 18–24 hours (monitored by TLC). After the completion of the reaction, THF was distilled off, and LC-MS of the crude reaction mixture was recorded, and it confirms the formation of 1-phenyl-2-morpholin-1-yl-ethane-1,2-dione (**2a**), along with *N*-hydroxymorpholine. The THF was distilled off from the reaction mixture up to 80% of the volume, and was subjected to aqueous acidic workup and extracted with dichloromethane. The organic layer was then separated, distilled off under reduced pressure, and the crude product was purified by column chromatography. The product **2a** was obtained as an off-white solid in 54% of yield, though TLC and NMR of the crude reaction mixture shows more than 80–85% of product formation. The product **2a** was characterized by means of IR and NMR spectroscopy and mass spectroscopy. This reaction has shown high acceleration in reaction rate when pure oxygen was purged directly into the reaction mass instead of air. Kim et al.[23] reported mechanistically a similar



1a 2a 3

Scheme 1

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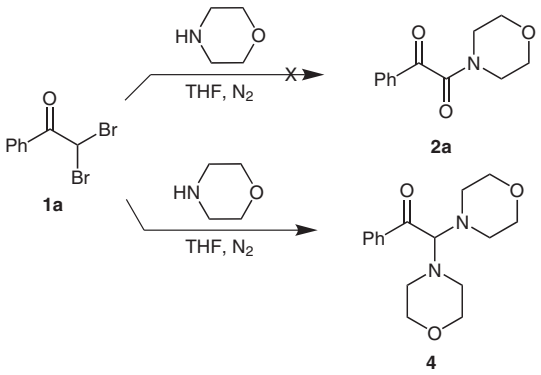


Scheme 2

transformation of dibromoethanone to α-keto amides in their thiadiazole synthesis.

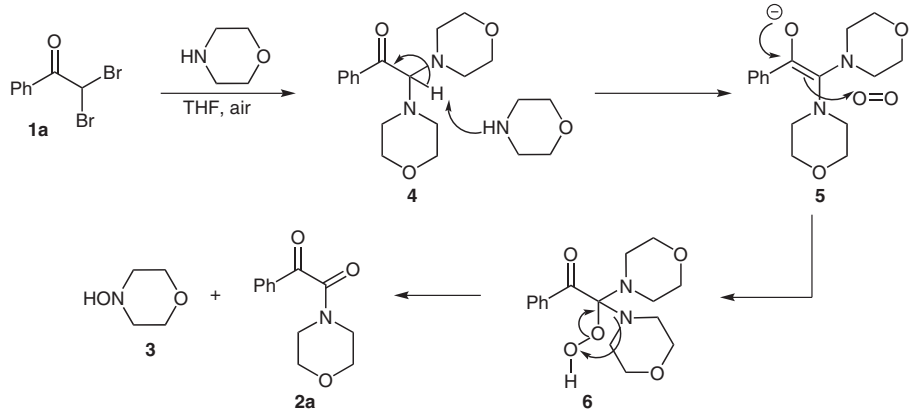
In order to confirm the formation of *N*-hydroxymorpholine as byproduct in the oxidative amidation reaction, a spiking experiment in the LC-MS column was conducted with freshly prepared standard sample of *N*-hydroxymorpholine with the crude reaction mixture without any work-up. The peak corresponds to *N*-hydroxymorpholine standard, and the molecular ion peak of 104 in the crude reaction mixture was eluted in the LC-MS column at the same retention time (RT) and relative retention time (RRT) with respect to the product **2a**. This result suggests that the formation of *N*-hydroxymorpholine might occur during the course of the reaction. However, our attempt to isolate pure *N*-hydroxymorpholine from the reaction mixture was not successful.

To understand the probable mechanism of the reaction, we have carried out the reaction under anaerobic conditions (Scheme 2). Thus, a mixture of dibromoethanone **1a** and morpholine in 1:4 molar ratio was stirred together at room temperature in dry THF under perfect anhydrous nitrogen blanket. After completion of the reaction (monitored by TLC, 8–10 h), the solvent was evaporated under vacuum. The crude reaction mass was analyzed both by LC-MS and NMR and confirms the formation of 1-phenyl-2,2-dipiperidin-1-yl-ethanone (**4**)[24] and no traces of α-keto amide were detected. The above result suggests that oxygen is essential for the oxidative amidation reaction, and the reaction might have proceeded through the diaminal **4** followed by aerial oxidation under basic conditions.

Based on the above observations, a plausible mechanism for the conversion of 2,2-dibromo-1-phenylethanone (**1a**) to phenyl α-keto amide **2a** is depicted in Scheme 3. The initial step of the reaction involves the formation of 1-phenyl-2,2-dimorpholin-yl-ethanone (**4**) by the nucleophilic displacement of both bromine atoms of dibromoketone **1a** by morpholine. Aminal **4** subsequently undergoes base-assisted enolization, followed by reaction with oxygen to form the intermediate **6**. The unstable intermediate **6** upon extrusion of *N*-hydroxymorpholine will result in the desired α-keto amide **2a**.

The generality of this oxidative amidation reaction was evaluated by screening the reaction of a series of dibromoethanones **1a–e** derived from aryl as well as heteroaryl ethanones with different secondary amines, and the results are summarized in Table 1.[25] All these reactions were performed in a 1:4 molar ratio of dibromoethanone (**1a–e**) and secondary amine in the presence of air, and the reactions were completed within 24 hours. The reactions performed with 2–3 mol equivalents of secondary amine took prolonged time (more than 72 h, in the case of **2a**) for completion. Hence no further attempts were made to optimize the reaction with lesser equivalents of secondary amine for this oxidative amidation reaction. The reaction of electron-rich and electron-poor aromatic and heterocyclic dibromoethanones with secondary amines afforded the expected α-keto amides in moderate to good yields. The attempt to synthesize dibenzyl and dibutyl α-keto-amides by the reaction of N,N'-dibenzyl and dibutyl amines with dibromoethanone were not successful, and these reactions resulted in unidentifiable product mixtures along with some percentage of unreacted starting materials. Similarly, our attempts to synthesis α-keto amides derived from *gem*-dibromo derivatives of aliphatic ketones under different reaction conditions were not successful, and these reactions resulted in inseparable product mixtures; the expected keto amides were not detected in LC-MS analysis.

Compounds that have been reported to be high affinity FKBP 12 ligands are pipecolyl or prolyl ketoamides.[27]



Scheme 3

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Table 1 Oxidative Amidation Reaction with Dibromoethanones **1a–e** and Different Secondary Amines

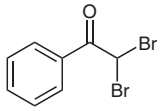
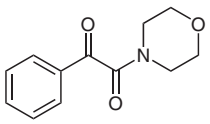
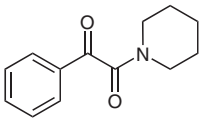
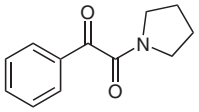
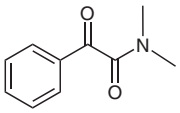
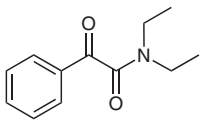
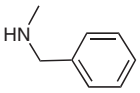
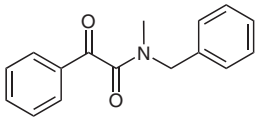
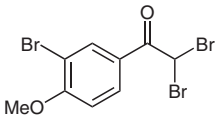
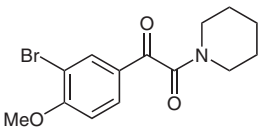
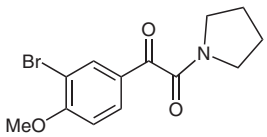
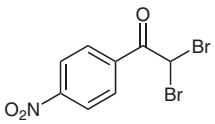
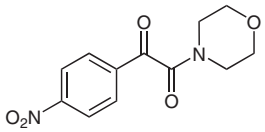
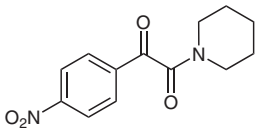
Entry	Dibromoethanone	Amine	α-Keto amide	Yield (%)	Mp (°C)
1	 **1a**		 **2a**	54[26a]	90–93
2	**1a**		 **2b**	52[17]	104–106
3	**1a**		 **2c**	54[17]	Viscous liquid
4	**1a**		 **2d**	48[26b]	Viscous liquid
5	**1a**		 **2e**	51[17]	Viscous liquid
6	**1a**		 **2f**	45[16e]	Viscous liquid
7	 **1b**		 **2g**	56	135–138
8	**1b**		 **2h**	57	120–122
9	 **1c**		 **2i**	60	143–146
10	**1c**		 **2j**	60[16h]	96–98

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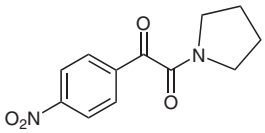
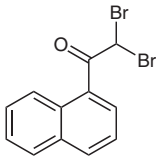
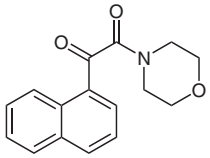
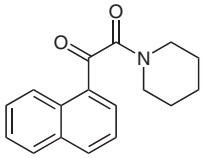
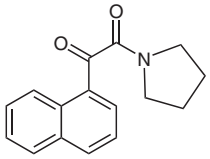
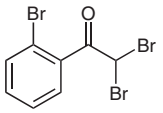
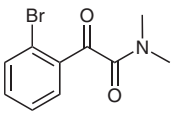
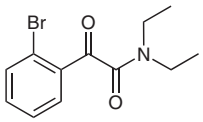
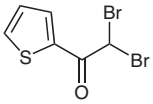
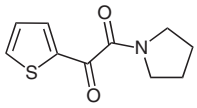
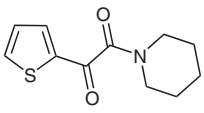
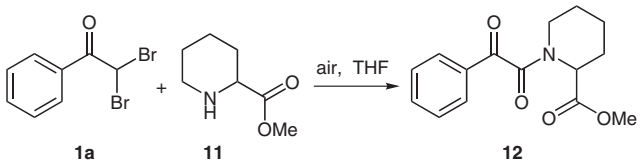
Table 1 Oxidative Amidation Reaction with Dibromoethanones **1a–e** and Different Secondary Amines (continued)

Entry	Dibromoethanone	Amine	α-Keto amide	Yield (%)	Mp (°C)
11	**1c**		 **2k**	59[16h]	115–117
12	 **1d**		 **2l**	55	123–125
13	**1d**		 **2m**	61	140–141
14	**1d**		 **2n**	55	126–128
15	 **1e**		 **2o**	45[26c]	Viscous liquid
16	**1e**		 **2p**	59[26c]	Viscous liquid
17	 **2f**		 **2q**	51[17]	85–88
18	**2f**		 **2r**	59[17]	130–132

Using the methodology developed for the synthesis of α-keto amides, we have attempted the reaction of 2,2-dibromo-1-phenylethanone (**1a**) with 2-pipecolyl methyl ester. The reaction between this cyclic amino acid ester and dibromoethanone **1a** resulted in the formation of expected product 1-(2-oxo-2-phenyl-acetyl)-piperidine-2-carboxylic acid methyl ester (**12**) in low yield (24%), along with unreacted starting material (Scheme 4). The product was isolated after usual acidic workup and column chromatographic purification.



1a **11** **12**

Scheme 4

Thus, by following relatively straightforward design elements, we have effectively designed an efficient method for the synthesis of α-keto amides; the present reaction

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promises to afford a generally applicable route for the synthesis of a variety of aromatic and heteroaromatic α-keto amides. The generality of the method was established by carrying out the reaction with aromatic and heteroaromatic ketones with cyclic and acyclic secondary amines as well as amino acid ester. The applications of this methodology for the synthesis of few biologically active natural products are in progress.

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(25) **Representative Procedure for the Synthesis of 1-Phenyl-2-morpholin-1-yl-ethane-1,2-dione**

To a solution of 2,2-dibromo-1-phenylethanone (**1a**, 1 g, 0.0035 mol, 1 equiv) in THF (10 mL) was added morpholine (0.99 g, 0.014 mol, 4 equiv) dropwise over a period of 30 min at 20–30 °C. The temperature of the reaction mixture was slowly raised to 40–50 °C under an oxygen atmosphere and maintained for 18–26 h (monitored by TLC). After the completion of the reaction, THF was distilled off up to 80% of its volume. The reaction mass was then diluted with CH_2Cl_2 (25 mL), washed with dil. HCl (10 mL, 4×), followed by brine. The organic layer was then dried over Na_2SO_4, and the product **2a** was obtained after column chromatographic purification in 54% of yield as off-white solid; yield 57%.

IR (KBr): 1428, 1517, 1578, 1604, 1683, 1677, 2843 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.40 (m, 2 H), 3.70 (m, 2 H), 3.80 (m, 4 H), 7.50 (m, 2 H), 7.70 (m, 1 H), 7.95 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.6, 46.2, 66.6, 66.7, 129.0, 129.6, 133.0, 134.8, 165.4, 191.1. MS: *m/z* (%) = 220.2 [M + 1], 192,159, 105. Anal. Calcd for $C_{12}H_{13}NO_3$ (219.9): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.71; H, 5.95; N, 6.32.

1-Phenyl-2-piperidin-1-yl-ethane-1,2-dione (2b)

Yield 52%. IR: (KBr): 1447, 1579, 1638, 1671, 2938 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.60 (m, 2 H), 1.71 (m, 4 H), 3.30 (m, 2 H), 3.71 (m, 2 H), 7.50 (m, 2 H), 7.64 (m, 1 H), 7.95 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.3, 25.4, 26.1, 42.1, 47.0, 128.9, 129.5, 133.2, 134.6, 165.4, 191.9. MS: *m/z* (%) = 218.1 [M + 1], 190.2, 149.0, 126.0. Anal. Calcd for $C_{13}H_{15}NO_2$ (203.4): C, 71.81; H, 6.96; N, 6.45. Found: C, 71.79; H, 6.91; N, 6.41.

1-Phenyl-2-pyrolidin-1-yl-ethane-1,2-dione (2c)

Yield 54%. IR (KBr): 1446, 1597, 1638, 1677, 2882, 2977 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.95 (m, 4 H), 3.38 (m, 2 H), 3.65 (m, 2 H), 7.49 (m, 2 H), 7.63 (m, 1 H), 7.95 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.8, 25.7, 45.0, 46.5, 128.7, 129.6, 132.7, 134.4, 165.8, 191.4. MS: *m/z* (%) = 204.1 [M + 1], 176.3, 105. Anal. Calcd for $C_{12}H_{13}NO_2$ (203.4): C, 70.92; H, 6.45; N, 6.89. Found: C, 70.89; H, 6.45; N, 6.89.

1-phenyl-2-dimethylamino-ethane-1,2-dione (2d)

Yield 48%. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.95 (s, 3 H), 3.11 (s, 3 H), 7.50 (m, 2 H), 7.63 (m, 1 H), 7.92 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.8, 36.9, 128.9, 129.5, 132.9, 134.6, 166.9, 191.7. MS: *m/z* (%) = 178.2 [M + 1], 150.2, 105.0. Anal. Calcd for $C_{12}H_{13}NO_3$ (177.2): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.24; N, 7.89.

1-phenyl-2-diethylamino-ethane-1,2-dione (2e)

IR (KBr): 720, 855, 1146, 1233, 1383, 1448, 1642, 1681, 1720, 2934, 2977 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.29 (m, 3 H), 1.31 (m, 3 H), 3.2 (m, 2 H), 3.59 (m, 2 H), 7.50 (m, 2 H), 7.63 (m, 1 H), 7.93 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.8, 14.0, 38.8, 42.1, 128.8, 129.5, 130.0, 133.0, 133.2, 134, 166.6, 191.4. MS: *m/z* (%) = 206.1 [M + 1], 178.1, 130. Anal.Calcd for $C_{12}H_{15}NO_2$ (205.1): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.19; H, 7.31; N, 6.80.

***N*-Benzyl-*N*-methyl-2-oxo-2-phenylacetamide (2f)**

IR (KBr): 723, 881, 1003, 1210, 1449, 1643, 1680, 2926, 3030, 3063 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.84–2.99 (d, 3 H), 4.39 (s, 1 H), 4.74 (s, 1 H), 7.20–7.61 (m, 8 H), 8.02–8.11 (m, 2 H), ^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.4, 49.8, 128.2, 128.7, 128.8, 128.9, 129.5, 130, 133, 133.2, 133.5, 134.6, 134.8, 135.7, 167, 191.3 MS: *m/z* (%) = 254.1 [M + 1], 211, 198. Anal. Calcd for $C_{15}H_{15}NO_2$ (253.1): C, 75.87; H, 5.97; N, 5.53. Found: C, 75.79; H, 5.96; N, 5.50.

1-(3-Bromo-4-methoxy-phenyl)-2-piperidin-1-yl-ethane-1,2-dione (2g)

Yield 56%. IR (KBr): 1202, 1278, 1405, 1589, 1637, 1671, 2927 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.28 (m, 4 H), 1.69 (m, 2 H), 3.30 (m, 2 H), 3.70 (m, 2 H), 3.98 (s, 3 H), 6.95 (d, 1 H, *J* = 8.6 Hz), 7.98 (dd, 1 H, *J* = 2.2, 8.6 Hz), 8.15 (d, 1 H, *J* = 2.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.2, 25.3, 26.1, 42.1, 47.0, 56.5, 111.4, 112.4, 127.3, 131.0, 134.5, 160.7, 164.9, 189.3. MS: *m/z* (%) = 326.10 [M + 1], 300.0, 212.8, 148.7, 112.1. Anal. Calcd for $C_{15}H_{20}BrNO_3$ (326.19): C, 51.55; H, 4.94; N, 4.29. Found: C, 51.53; H, 4.28; N, 4.83.

1-(3-Bromo-4-methoxy-phenyl)-2-pyrolidin-1-yl-ethane-1,2-dione (2h)

Yield 57%. IR (KBr): 1264, 1499, 1589, 1629, 1642, 1665, 2980 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.95 (m, 4 H), 3.40 (m, 2 H), 3.70 (m, 2 H), 3.98 (s, 3 H), 6.95 (d, 1 H, *J* = 8.8 Hz), 7.98 (dd, 1 H, *J* = 2.2, 8.8 Hz), 8.2 (d, 1 H, *J* = 2.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.9, 25.8, 45.2, 46.7, 56.5, 111.3, 112.3, 127.0, 131.4, 135.0, 160.7, 164.3, 188.9. MS: *m/z* (%) = 313.90 [M + 1], 312.0 [M^+], 212.9, 134.8. Anal. Calcd for $C_{13}H_{14}BrNO_3$ (312.36): C, 50.02; H, 4.52; N, 4.49. Found: C, 50.0; H, 4.51; N, 4.43.

1-Naphthalen-1-yl-2-morpholin-1-yl-ethane-1,2-dione (2l)

IR (KBr):1115.7, 1226, 1252, 1273, 1628, 1669, 2923 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.43 (m, 2 H), 3.65 (m, 2 H), 3.83 (m, 4 H), 7.60 (m, 3 H), 8.01 (m, 3 H), 9.20 (d, 2 H, *J* = 8.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.5, 46.2, 66.4, 124.3, 125.5, 126.9, 128.2, 128.6, 129.3, 130.7, 133.9, 134.3, 136.0, 165.9, 193.4 MS: *m/z* (%) = 270.1 [M + 1], 249, 177.4, 155.2. Anal. Calcd for $C_{16}H_{15}NO_3$ (269.11): C, 71.36; H, 5.61; N, 5.20. Found: C, 71.30; H, 5.93; N, 5.52.

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