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Silver-Catalyzed Decarboxylative Radical Addition/Cyclization of Oxamic Acids with Alkenes towards Quinolin-2-ones

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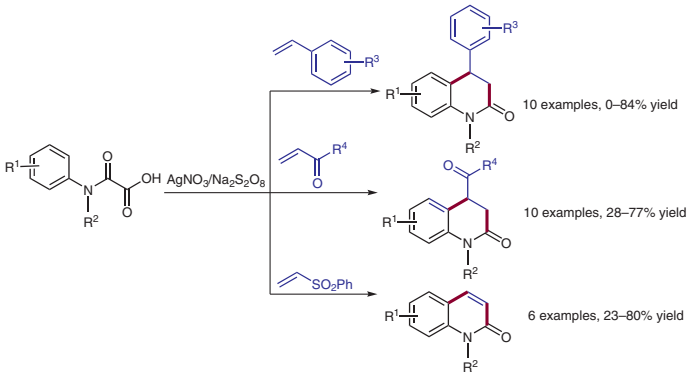


Received: 16.04.2020
Accepted after revision: 21.05.2020
Published online: 21.07.2020
DOI: 10.1055/s-0040-1707891; Art ID: st-2020-u0216-l
Crowd-Reviewed

Abstract An efficient silver-catalyzed tandem decarboxylative radical addition/cyclization of oxamic acids with alkenes has been developed. This method provides a novel and straightforward protocol toward a variety of 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones, 4-(α-carbonyl)-3,4-dihydroquinolin-2(1*H*)-ones, and quinolin-2(1*H*)-ones in aqueous solution.

Key words silver catalysis, addition, cyclization, tandem reaction, oxamic acids, quinolinones

Quinolin-2-one is a common and important N-heterocyclic skeleton that is widely found in natural products, commercial drugs, and bioactive molecules (Figure 1).[1] Moreover, quinolin-2-ones are versatile precursors for synthesizing 2-aminoquinolines, 2-alkoxyquinolines, 2-haloquinolines, and other useful quinoline derivatives.[2] In this context, it is highly desirable to develop easily operable and highly effective methods for the construction of quinolin-2-ones. In recent decades, a great deal of research has been

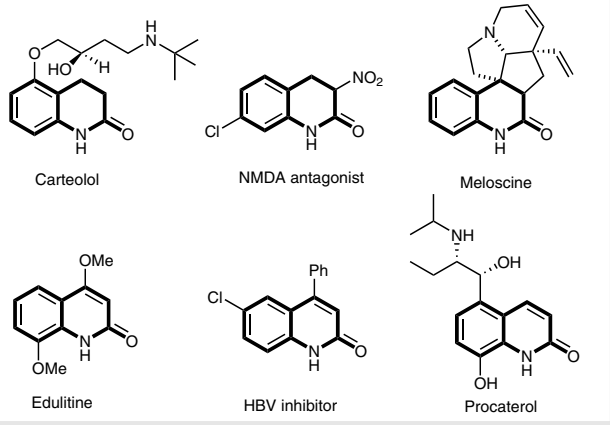
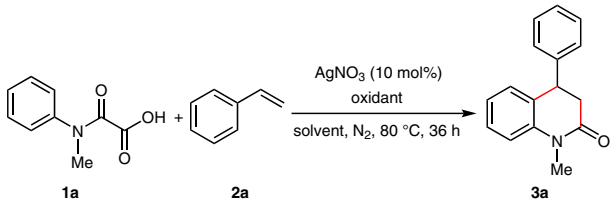


Figure 1 Several representative compounds containing quinolin-2-one scaffolds

Table 1 Screening of the Reaction Conditions[a]



Entry	Oxidant (equiv)	Solvent	Yield[b] (%)
1	$K_2S_2O_8$ (2.0)	1:1 MeCN–H_2O	45
2	**$Na_2S_2O_8$ (2.0)**	**1:1 MeCN–H_2O**	**65**
3	$(NH_4)_2S_2O_8$ (2.0)	1:1 MeCN–H_2O	60
4	TBHP (2.0)	1:1 MeCN–H_2O	0
5	$Na_2S_2O_8$ (1.0)	1:1 MeCN–H_2O	41
6	$Na_2S_2O_8$ (3.0)	1:1 MeCN–H_2O	16
7	$Na_2S_2O_8$ (2.0)	1:1 DMSO–H_2O	36
8	$Na_2S_2O_8$ (2.0)	1:1 THF–H_2O	30
9	$Na_2S_2O_8$ (2.0)	1:1 toluene–H_2O	18
10	$Na_2S_2O_8$ (2.0)	1:1 acetone–H_2O	31
11	$Na_2S_2O_8$ (2.0)	1:1 CH_2Cl_2–H_2O	17
12	$Na_2S_2O_8$ (2.0)	MeCN	0
13	$Na_2S_2O_8$ (2.0)	H_2O	<5
14[c]	$Na_2S_2O_8$ (2.0)	1:1 MeCN–H_2O	0
15[d]	–	1:1 MeCN–H_2O	0

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), $AgNO_3$ (0.03 mmol, 10 mol%), solvent (3.0 mL), oxidant, under N_2, 80 °C, 36 h.
[b] Isolated yield.
[c] Without the catalyst.
[d] Without the oxidant.

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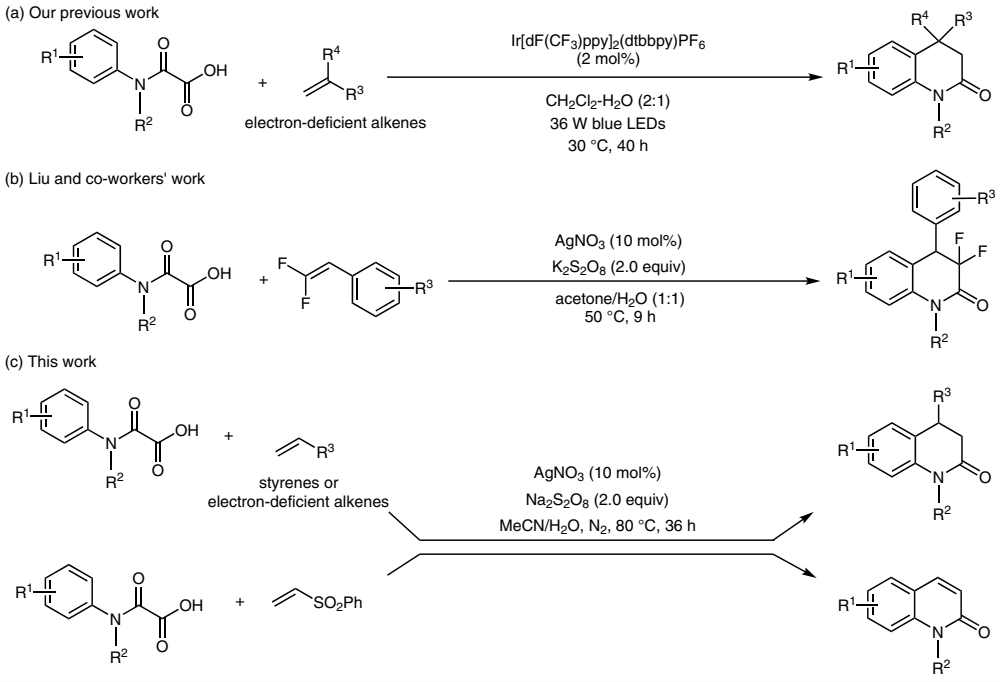
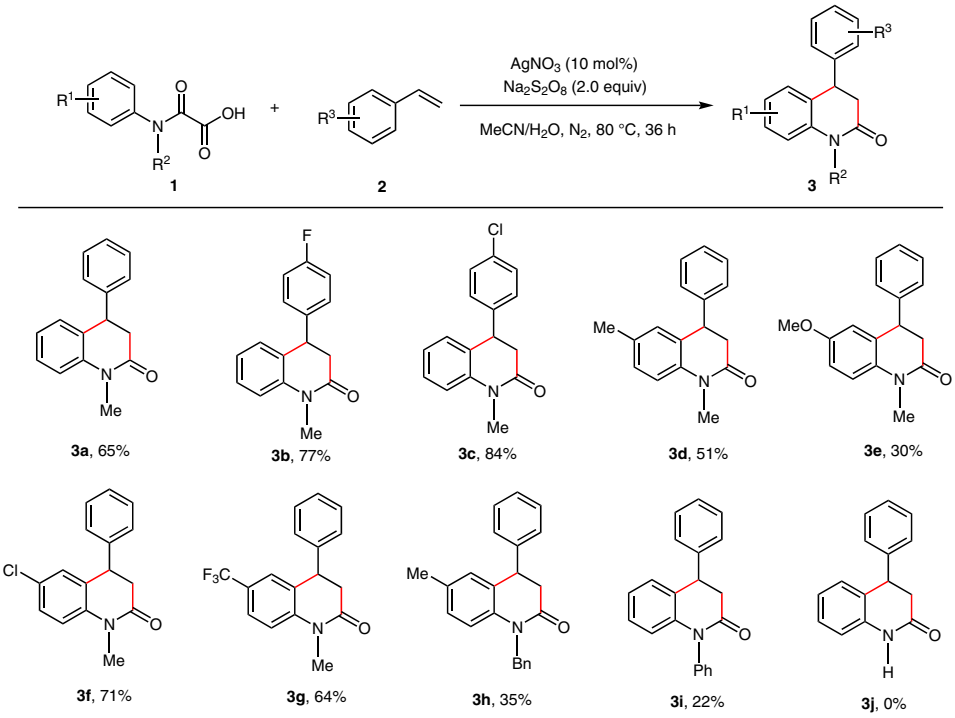
conducted on the synthesis of quinolin-2-ones, and various effective preparation methods, such as intramolecular Friedel–Crafts reactions, transition-metal-catalyzed tandem cyclizations, or radical addition/ring formation reactions, have been developed.[3–5] In particular, in the last ten years the radical addition/6-*endo*-*trig*-cyclization of cinnamamides has infused new vigor into the synthesis of quinolin-2-ones.[5] Although this strategy has shown good performance in the construction of 3,4-disubstituted dihydroquinolinones, it suffers from a limited substrate scope and cannot directly synthesize 3,4-unsubstituted or monosubstituted quinolin-2-ones. Therefore, direct and efficient methods for constructing such compounds remain highly desirable.

Carbamoyl radicals are key synthetic intermediates that play an important role in the synthesis of isocyanates, amides, and nitrogenous heterocyclic compounds.[6–8] In recent years, the synthesis of substituted quinolin-2-ones through *N*-arylcarbamoyl radical addition/cyclization has attracted particular attention. Petersen and co-workers reported a photoredox-catalyzed single-electron-reductive decarboxylation of *N*-hydroxyphthalimidooxamides to produce *N*-arylcarbamoyl radicals that undergo an addition/cyclization reaction with electron-deficient alkenes to form 3,4-dihydroquinolin-2-one architectures.[9] As carbamoyl radical precursors, compared with *N*-hydroxyphthalimidooxamides, oxamic acids have advantages in terms of atom economy, greenness, and ease of preparation. Our group previously generated *N*-arylcarbamoyl radicals from *N*-arylcarbamoyl acids through visible-light-mediated oxidative decarboxylation and then reacted them with electron-deficient alkenes to give quinolin-2-ones (Scheme 1a).[10] Recently, Wang's group reported a decarboxylative lactamization of 2-vinylphenyloxamic acids mediated by hypervalent iodine(III), involving a ring-strain-permitted radical decarboxylation process.[11] Liu and co-workers recently reported an approach to the construction of CF_2-containing 3,4-dihydroquinolin-2-ones through the decarboxylative radical addition/cyclization of oxamic acids with *gem*-difluoroolefins (Scheme 1b).[12] Despite the advances made in this area, the scope of the alkene substrates is very limited and considerable challenges remain in the reactions of electron-rich olefins with *N*-arylcarbamoyl radicals and in the synthesis of 3,4-unsubstituted quinolinones by a radical pathway. We recently filed two patents on the preparation of 3,4-dihydroquinolin-2(1*H*)-ones from oxamic acids by Ag catalysis.[13] Here, we provide full details of the reaction development; we also further explore the scope of the reaction, particularly in terms of various substituted *N*-arylcarbamoyl radical precursors and alkenes, and we introduce an extension of the original approach for synthesis of the quinolin-2(1*H*)-ones under our optimized reaction conditions (Scheme 1c).

We began our investigations by reacting *N*-methyl-*N*-phenyloxamic acid (**1a**) with styrene (**2a**) as model substrates to identify the optimal reaction conditions (Table 1). Gratifyingly, in the presence of simple $AgNO_3$ (10 mol%) as a catalyst and $K_2S_2O_8$ (2.0 equiv) as an oxidant in 1:1 MeCN–H_2O at 80 °C, the reaction gave the desired product **3a** in 45% yield after 36 hours (Table 1, entry 1). The choice of ox-

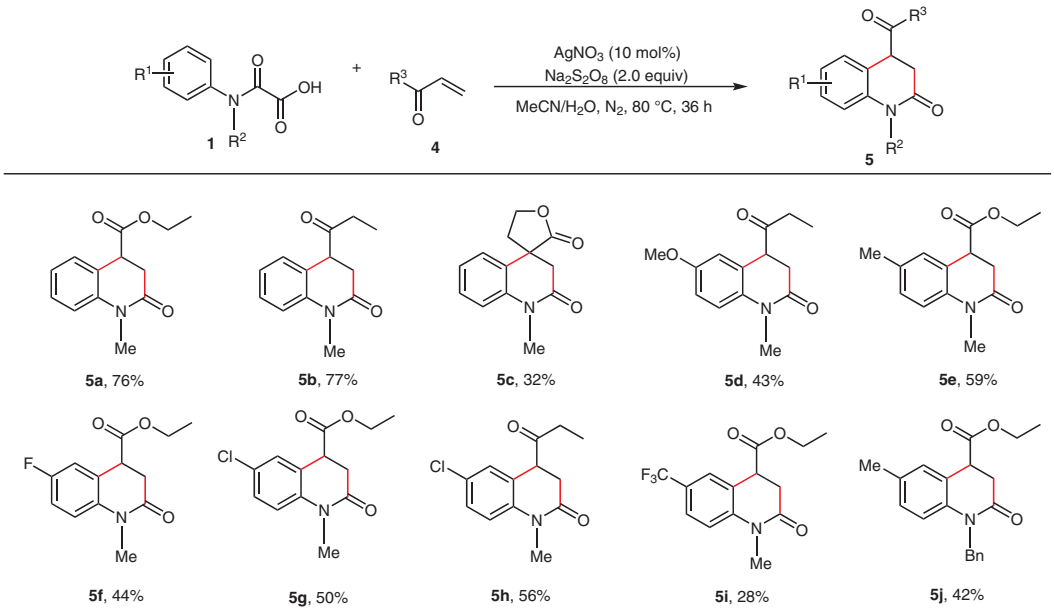


Scheme 1 Decarboxylative tandem cyclizations of oxamic acids with alkenes for synthesizing quinolin-2-ones



Scheme 2 Decarboxylative tandem cyclization of oxamic acids with styrenes

idant was found to have a dramatic effect on the yield (entries 2–4). Among the oxidants tested, $Na_2S_2O_8$ was found to be the most efficient in this transformation, and the yield of the desired product was increased to 65% (entry 2). Reducing or increasing the amount of the $Na_2S_2O_8$ did not improve the yield of **3a** (entries 5 and 6). Additionally, changing the solvent to DMSO–H_2O, THF–H_2O, toluene–H_2O, acetone–H_2O, CH_2Cl_2–H_2O, MeCN, or H_2O led to lower yields of



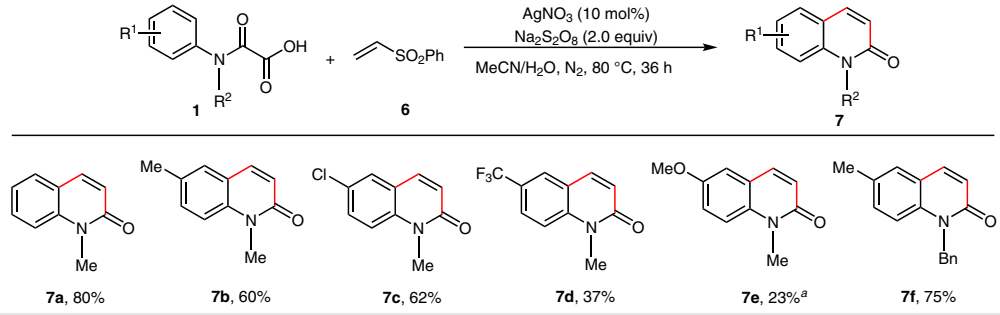
Scheme 3 Decarboxylative tandem cyclization of oxamic acids with electron-deficient alkenes

3a (entries 7–13). Controlled experiments confirmed that the reaction did not occur in the absence of $AgNO_3$ or $Na_2S_2O_8$ (entries 14 and 15).

With the optimized reaction conditions in hand, we started to investigate the substrate scope of the radical cyclization reaction with various substituted oxamic acids and styrenes (Scheme 2). To our satisfaction, the optimized conditions were found to be generally applicable for *p*-fluorostyrene and *p*-chlorostyrene, providing products **3b** and **3c** in yields of 77 and 84%, respectively. The reaction was compatible with methyl, methoxy, chloro, and trifluoromethyl functional groups on the aromatic ring of the oxamic acid; both electron-rich and electron-deficient oxamic acids reacted effectively with styrene to give the desired products **3e–g** in yields of 30–71%. In addition, an N-benzyl-protected oxamic acid was also accommodated by this reaction system, and the corresponding product **3h** was obtained in 35% yield. When an *N*-phenyl-protected oxamic acid reacted with styrene, two products were formed: 1,4-diphenyl-3,4-dihydroquinolin-2(1*H*)-one (**3i**) in 22% yield and the radical rearrangement product *N*,3,3-triphenylpropanamide (**3i′**) in 23% yield (see Supporting Information). Unfortunately, the oxamic acid lacking an N-protecting group did not undergo this conversion (**3j**).

To further test the applicability of this protocol, the scope of the electron-deficient alkene was explored (Scheme 3). Various substituted electron-deficient alkenes, such as ethyl acrylate, ethyl vinyl ketone, and α-methylene-γ-butyrolactone displayed good reactivities in this transformation, giving the desired products **5a–c** in yields of 32–77%. Oxamic acids with either electron-donating or electron-withdrawing groups were also well tolerated in the same fashion, and afforded the corresponding products **5d–i** in moderate yields. Moreover, an N-benzyl-substituted oxamic acid also reacted efficiently with ethyl acrylate to give the 3,4-dihydroquinolin-2(1*H*)-one **5j** in 42% yield.

To our surprise, the reaction between phenyl vinyl sulfone and oxamic acids in the presence of the $AgNO_3/Na_2S_2O_8$ catalytic system gave completely different results to those obtained by using our previous photocatalytic system.[10] 4-(Phenylsulfonyl)-3,4-dihydroquinolin-2(1*H*)-ones were not obtained; instead quinolin-2(1*H*)-ones **7a–f** were obtained in isolated yields of 23–80% (Scheme 4). We speculate that the original target products, the 4-(phenylsulfo-



Scheme 4 Reaction of oxamic acids with phenyl vinyl sulfone to give quinolin-2(1*H*)-ones. [a] At 90 °C for 48 h.

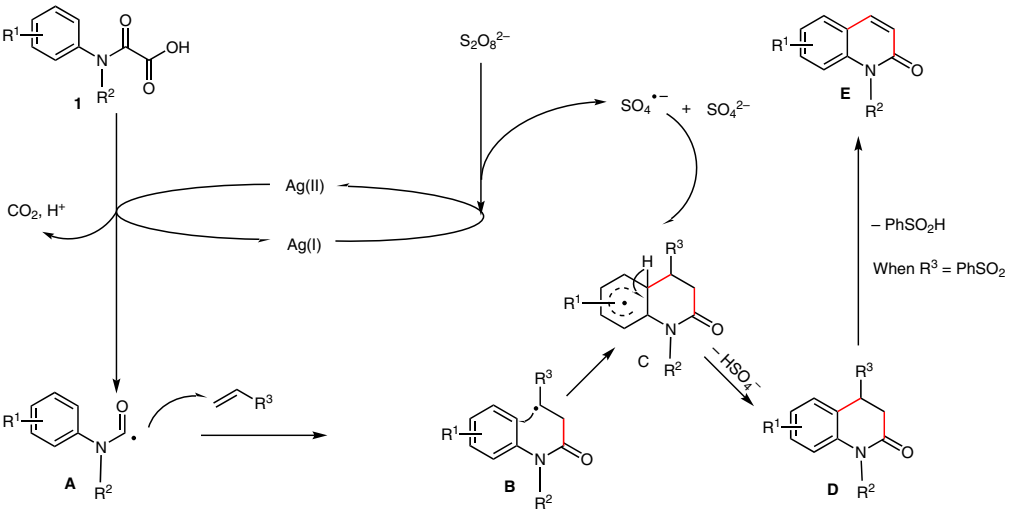


Figure 2 Proposed reaction mechanism

nyl)-3,4-dihydroquinolin-2(1*H*)-ones, undergo an additional classical Julia–Lythgoe elimination at high temperature to form the corresponding quinolin-2(1*H*)-ones.

Based on the present results and related reports in the literature,[6,10–12] a plausible reaction mechanism is proposed as shown in Figure 2. First, Ag(I) is oxidized by persulfate anion to form Ag(II), which then triggers a single-electron-transfer process of the *N*-aryloxamic acid **1** to regenerate the Ag(I) and form the *N*-arylcarbamoyl radical **A** with release of CO_2. Subsequently, the *N*-arylcarbamoyl radical **A** adds to the alkene to form radical intermediate **B**, which undergoes an intramolecular cyclization to produce radical **C**. Radical **C** then undergoes an oxidative single-electron-transfer/deprotonation/aromatization sequence to give corresponding product **D**. In addition, it is noteworthy that when phenyl vinyl sulfone is used, the quinolin-2(1*H*)-one **E** is obtained as the final product through a Julia–Lythgoe elimination reaction of **D**.

In conclusion, we have developed a practical silver-catalyzed tandem decarboxylative radical addition/cyclization of oxamic acids with alkenes to give various 4-aryl-3,4-dihydroquinolin-2(1*H*)-ones, 4-(α-carbonyl)-3,4-dihydroquinolin-2(1*H*)-ones, or quinolin-2(1*H*)-ones in aqueous solution.[14] This general protocol features mild reaction conditions and a broad range of easily accessible substrates.

Funding Information

Financial support from the National Natural Science Foundation of China (21302130 and 21676166), the Science and Technology Department of Zhejiang Province (2014C31141 and LGG20B060002), and the Department of Education of Zhejiang Province (Y201941045) are acknowledged with thanks.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707891.

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(14) **Quinolin-2(1*H*)-ones 3, 5, and 7; General Procedure**

A 10 mL reaction vial was charged sequentially with the appropriate oxamic acid **1** (0.3 mmol, 1.0 equiv), $AgNO_3$ (0.03 mmol, 10 mol%), $Na_2S_2O_8$ (0.6 mmol, 2.0 equiv), MeCN (1.5 mL), and H_2O (1.5 mL). The vial was closed and bubbled with N_2 for 5 min. The appropriate alkene **2**, **4**, or **6** (0.9 mmol, 3.0 equiv) was then injected into the vial, and the mixture was stirred at 80 °C for 36 h. The resulting mixture was diluted with EtOAc (40 mL) and H_2O (10 mL), and the organic layer was recovered, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc–PE).

6-Chloro-1-methyl-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one (3f)

Colorless oil; yield: 57.7 mg (71%; 0.3 mmol scale). IR (film): 2928, 1676, 1491, 1416, 1360, 1267, 1130 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 2 H), 7.30–7.23 (m, 2 H), 7.15–7.13 (m, 2 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.87 (dd, *J* = 2.0, 0.4 Hz, 1 H), 4.19 (t, *J* = 7.2 Hz, 1 H), 3.36 (s, 3 H), 2.95 (d, *J* = 3.6 Hz, 1 H), 2.93 (d, *J* = 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 140.2, 139.0, 131.0, 129.1, 128.4, 128.0, 127.8, 127.5, 116.2, 41.4, 38.5, 29.7. GC/MS: *m/z* (%) = 228 (68), 271 (100) [M^+].