Zinc Perchlorate Hexahydrate Catalysed Conjugate Addition of Thiols to α,β-Unsaturated Ketones

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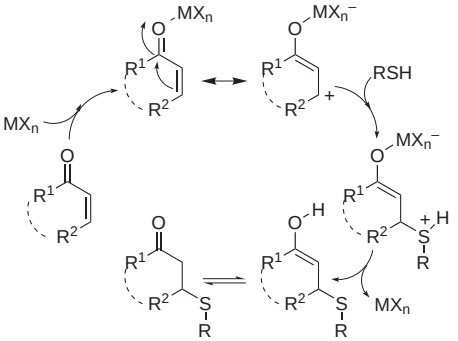
Abstract: Zn(II) perchlorate hexahydrate has been found to be a new and efficient catalyst for conjugate addition of thiols to α,β-unsaturated ketones under solvent-free conditions at room temperature. The reaction of aryl, arylalkyl and alkyl thiols with cyclic and acyclic α,β-unsaturated ketones takes place affording excellent yields after five minutes to six hours. The compatibility of $Zn(ClO_4)_2 \cdot 6H_2O$ with different solvents provides a means to carry out the reaction under versatile experimental conditions. The rate of thiol addition was dependent on the electronic and steric factors of the enones and the thiols. The substituent at the β-carbon of the α,β-unsaturated ketone substrate caused steric hindrance during conjugate addition and required longer reaction times. The rate of reaction for alkane thiols e.g. ethanethiol was sluggish compared to that of aryl thiols.

Keywords: conjugate addition, thiol, α,β-unsaturated ketone, zinc(II) perchlorate, catalyst

Thia-Michael addition is an important transformation due its important role in biosynthesis[1] as well as in the synthesis of bioactive compounds.[2] The reaction has versatile applications in synthetic organic chemistry. The ease of generation of the double bond by removal of the sulfur moiety either by copper(I)-induced elimination[3] or by oxidative elimination,[2b] offers an elegant strategy for chemoselective protection of the olefinic double bond of conjugated enones.[2b] It is known that β-sulfido carbonyl compounds, derived from thia-Michael addition to α,β-unsaturated carbonyl compounds, serve as starting materials for the generation of β-acylvinyl cation equivalents[4] and homoenolate equivalents.[5] These are of interest to organic/medicinal chemists for the development of new methodologies for thia-Michael additions. Various catalysts have been used for the conjugate addition of thiols to α,β-unsaturated carbonyl compounds. These include metal halides,[6] nitrate,[7] phosphates,[8] triflates,[9] solid acids,[10] and ionic liquids.[11] The various disadvantages (e.g. long reaction times,[6a,b,9a] use of halogenated solvents,[6b,7,9a] difficulty in recovery of high boiling solvents,[10b] high temperatures,[10b,11c] special efforts required for preparation of catalysts,[8,9b] use of costly catalysts,[6b,9,11a] moderate yields,[6b,7] use of toxic chemicals,[6a] etc.) encountered in the reported methodologies necessitate the development of a better method.

We felt that the use of a metal catalyst that can form a strong coordinate bond with the carbonyl oxygen of the α,β-unsaturated ketones should increase the electrophilicity of the β-carbon and assist the conjugate addition to be carried out under milder conditions and in short reaction times (Scheme 1).



Scheme 1 Role of metal salts in catalyzing thia-Michael addition.

While designing a cheap and effective catalyst, we considered the following aspects: (i) the catalyst should be derived from group I/II metals so as to reduce its cost, (ii) the central metal ion of the metal salt should have strong oxophilic property for more effective coordinate bond formation with the carbonyl oxygen, and (iii) the counter anion should be highly electron-withdrawing in nature to make the central metal ion more oxophilic. While selecting suitable group I/II metal salts, we thought that the metal ion of salts of strong protic acids should have a more pronounced oxophilic property. Triflic acid is the strongest protic acid due to the large negative H_0 value (–14.1)[12] and perchloric acid is the second strongest protic acid. Recently it has been demonstrated that the perchlorate counter anion increased the oxophilicity of the central metal ion of metal perchlorates and made them highly efficient catalysts for electrophilic activation during acetylation.[13] Thus, we planned to evaluate the catalytic efficiency of various commercially available group I and II metal triflates and perchlorates and report that zinc perchlorate hexahydrate is a new and efficient catalyst for the thia-Michael addition.

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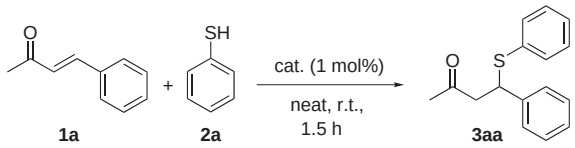


Scheme 2 Conjugate addition of **1a** with **2a** under the catalytic influence of various group I and II metal perchlorates and triflates.

In a model reaction, *trans*-4-phenyl-3-butene-2-one (**1a**) (2.5 mmol) was taken as a representative α,β-unsaturated carbonyl compound; this was treated with thiophenol (**2a**) (1.1 equiv) in the presence of various group I and II metal triflates and perchlorates under neat conditions at room temperature (Scheme 2).

The reactions were monitored by IR and GCMS and the optimum results are provided in Table 1.

Table 1 Reaction of **1a** with **2a** in the Presence of Various Perchlorates and Triflates[a]

Entry	Catalyst (1 mol%)	Yield (%)[b]
1	$LiClO_4$	48
2	$Mg(ClO_4)_2$	51
3	$Mg(ClO_4)_2·6H_2O$	45
4	$Ba(ClO_4)_2$	31
5	$Zn(ClO_4)_2·6H_2O$	92
6	$Mg(OTf)_2$	32
7	$Zn(OTf)_2$	83

[a] The substrate (1 equiv) was treated with thiophenol (1.1 equiv) in the presence of catalyst (1 mol%) at r.t. (ca. 25–30 °C) in the absence of solvent for 1.5 h.
[b] GCMS yield of the corresponding conjugate addition product **3aa**.

The best result was obtained in the presence of $Zn(ClO_4)_2·6H_2O$ (1 mol%) affording 92% conversion to the desired conjugate addition product **3aa** after 1.5 hours (Table 1, entry 5). The poor catalytic activity of $LiClO_4$ and $Ba(ClO_4)_2$ is probably due to the lower charge to size (Z^2/r) value of Li^+ (1.35 e^2m^{-10}) and Ba^{2+} (2.94 e^2m^{-10}) ions compared to that of Zn^{2+} ion (15.33 e^2m^{-10}).[14] The oxophilicity of Li^+ and Ba^{2+} ions became significantly lower compared to that of Zn^{2+} ion as a result of lower Z^2/r values of the former ions. The parallels between the catalytic activity and charge-size function of metal perchlorates was also observed during the metal perchlorate-catalysed acetylation[13c] and Diels–Alder reaction.[15] However, the inferior results obtained for $Mg(ClO_4)_2$ (Table 1, entry 2) and $Mg(ClO_4)_2·6H_2O$ (Table 1, entry 3) are probably due to the higher hydrolysis constant (pK_h value) of 11.42 for the Mg^{2+} ion compared to a value of 9.6 for the Zn^{2+} ion.[16] Thus, the magnesium salts became susceptible to hydrolytic decomposition in the presence of trace amounts of moisture and lost their catalytic property.[13d] The decrease in catalytic activity of $Mg(ClO_4)_2·6H_2O$ compared to that of $Mg(ClO_4)_2$ (Table 1, compare the results of entries 2 and 3) indicated the sensitivity of Mg^{2+} derived catalysts to non-anhydrous conditions. Surprisingly, magnesium and zinc triflates were found to be inferior to the corresponding perchlorates (Table 1, compare the result of entry 6 with those of entries 2 and 3 and the result of entry 7 with that of entry 5). A similar observation was made during the acetylation reaction.[13c]

We next planned to determine the influence of solvents on the catalytic property of $Zn(ClO_4)_2·6H_2O$ during the reaction of **1a** with **2a** (Table 2). The catalyst was compatible with non-polar (entry 5), weakly polar (Table 2, entries 1, 6 and 8), aprotic polar (Table 2, entries 3, 7, 9 and 10) and protic polar (Table 2, entry 11) solvents affording moderate to high yields. The results revealed that $Zn(ClO_4)_2·6H_2O$ retained its catalytic activity in solvents with poor (Table 2, entry 5) and weak (Table 2, entries 1, 3, 6, 8, 9 and 10) coordinating properties. The poor catalytic activity in MeCN (Table 2, entry 4) is probably due to competitive coordination of the solvent with the catalyst. The inferior results obtained in DMF are probably due to its specific affinity towards cations, which interferes with the formation of a coordinate bond between the carbonyl oxygen atom and Zn^{2+} ion. Although a similar interference of coordination between the carbonyl substrate and the Zn^{2+} ion is expected to take place in MeOH, the hydrogen bonding effect of MeOH probably compensates for this. The poor result obtained in water is due to the poor solubility of **1a** and **2a** in water.

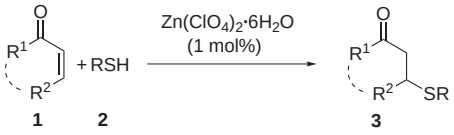
Table 2 Reaction of **1a** with **2a** in Various Solvents under the Catalytic Influence of $Zn(ClO_4)_2·6H_2O$[a]

Entry	Solvent	Yield (%)[b,c]
1	$(CH_2)_4O$	63
2	H_2O	17
3	EtOAc	66
4	MeCN	54
5	C_6H_{14}	75
6	Et_2O	77
7	Me_2NCHO	60
8	$(CH_2CH_2)_2O_2$	81
9	CH_2Cl_2	70
10	$MeNO_2$	75
11	MeOH	84

[a] Conditions: **1a** (2.5 mmol) was treated with **2a** (1.1 equiv) in the presence of $Zn(ClO_4)_2·6H_2O$ (1 mol%) at r.t. (~25–30 °C) for 1.5 h.
[b] GCMS yield of the corresponding conjugate addition product **3aa**.
[c] GCMS revealed the presence of unreacted **1a** and **2a**.

To establish the generality of this process, various enones such as **1a**, 2-cyclohexen-1-one (**1b**), 3-buten-2-one (**1c**) and *trans*-1,3-diphenylpropenone (**1d**) were treated with a range of aryl thiols e.g., **2a**, 4-methylthiophenol (**2b**),

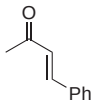
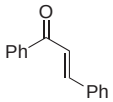
arylalkyl thiols e.g., benzyl thiol (**2c**), 2-furfuryl thiol (**2d**) and alkyl thiols e.g. ethane thiol (**2e**) under the above-described optimum conditions (Scheme 3). Excellent results were obtained in each case. The reactions were completed within five minutes to six hours (TLC, IR, GCMS) (Table 3). After the addition of the catalyst to the magnetically stirred mixture of the enone and the thiol, an exothermic reaction took place indicating product formation.



Scheme 3 Conjugate addition of various thiols to cyclic and acyclic enones under the catalytic influence of $Zn(ClO_4)_2 \cdot 6H_2O$.

The conjugate addition reaction of thiols, catalysed by $Zn(ClO_4)_2.6H_2O$, was found to be dependent on steric and electronic factors of the α,β-unsaturated ketones and thiols. The comparison of the results of **1b** and **1c** with those of **1a** and **1d** reveal that the substituent at the β-position of the enone exhibited steric and electronic effects. The reaction of **1a** with certain thiols took longer compared to the corresponding reaction with **1c** carried out under similar conditions (Table 3, compare the results of entries 1–5 with those of entries 11–15). This may be due to the steric hindrance exhibited by the 2-phenyl group of **1a** towards the approaching thiol. Furthermore, the π-resonance effect of the 2-phenyl substituent in **1a** and **1d** makes these enones less electrophilic compared to **1b** and **1c**. The combined steric and resonance effects of the 2-phenyl substituent make the conjugate addition reactions of **1a** and **1d**, with particular thiols, sluggish compared to those of **1b** and **1c** (Table 3, compare the results of entries 6–10 and 11–15 with those of entries 1–5 and 16–20). The comparison of the results of **1a** with those of **1d** suggested that the R^1 group of the α,β-unsaturated ketone exhibited electronic effects in controlling the conjugate addition. The resonance (hyperconjugative) effect of the methyl group in **1a** (R^1 = Me) increased the electron density at the carbonyl oxygen and enhanced the coordinating ability with the Zn^{2+}. Contrary to this, the phenyl group in **1d** (R^1 = Ph), decreased the electron density at the carbonyl oxygen by inductive and resonance effects and resulted in weak coordination between the carbonyl oxygen and the Zn^{2+}. Therefore, the reaction of **1d** with thiols required a longer time and higher temperature compared to the corresponding reaction of **1a** (Table 3, compare the results of entries 1–5 with those of entries 16–20). The longer times required for the conjugate addition of **2e**, an aliphatic thiol, represented the generalised steric effect of the thiol (Table 3, compare entry 5 with entries 1–4, entry 10 with entries 5–9, entry 15 with entries 11–14 and entry 20 with entries 16–19). The reaction rates of a six-membered cyclic enone without a β-substituent, exhibited parallels with those of an analogous acyclic enone having an unsubstituted β-carbon (Table 3, compare the results of entries 11–15 with those of entries 6–10).

Table 3 $Zn(ClO_4)_2 \cdot 6H_2O$-Catalysed Conjugate Addition of Thiols to α,β-Unsaturated Ketones[a]

Entry	Enone	Thiol	Product	Time (min)	Yield (%)[b,c]
					
1	**1a**	Thiophenol (**2a**)	**3aa**	90	89[d]
2	**1a**	4-Methylthiophenol (**2b**)	**3ab**	120	80
3	**1a**	Benzyl thiol (**2c**)	**3ac**	120	82
4	**1a**	2-Furfuryl thiol (**2d**)	**3ad**	120	78
5	**1a**	Ethane thiol (**2e**)	**3ae**	360	83
					
6	**1b**	**2a**	**3ba**	5	90
7	**1b**	**2b**	**3bb**	15	85
8	**1b**	**2c**	**3bc**	10	91
9	**1b**	**2d**	**3bd**	20	88
10	**1b**	**2e**	**3be**	20	82
					
11	**1c**	**2a**	**3ca**	5	84
12	**1c**	**2b**	**3cb**	10	81
13	**1c**	**2c**	**3cc**	10	83
14	**1c**	**2d**	**3cd**	15	80
15	**1c**	**2e**	**3ce**	20	81
					
16	**1d**	**2a**	**3da**	90	87[e]
17	**1d**	**2b**	**3db**	150	85[e]
18	**1d**	**2c**	**3dc**	150	91[e]
19	**1d**	**2d**	**3dd**	140	92[e]
20	**1d**	**2e**	**3de**	240	88[e]

[a] The enone (1 equiv) was treated with the thiol (1.1 equiv) in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ (1 mol%) at r.t. (ca. 25–30 °C except for entries 16–20) in the absence of solvent (except for entries 16–20).
[b] Isolated yield of the corresponding conjugate addition product obtained after chromatographic purification.
[c] The products were characterized by IR spectroscopy, NMR spectroscopy and MS.
[d] A 85% yield was obtained in carrying out the reaction in MeOH at r.t. for 1.5 h.
[e] The reaction was carried out in MeOH under reflux.

To compare the catalytic efficiency of $Zn(ClO_4)_2 \cdot 6H_2O$ with that of reported catalysts, we chose a few representative examples involving the same reactants and the results are summarized in Table 4. The results established that $Zn(ClO_4)_2 \cdot 6H_2O$ is a better suited for conjugate addition of thiols to α,β-unsaturated ketones with respect to (i) amount of catalyst, (ii) range of solvents, (iii) reaction times, (iv) reaction temperatures and (v) product yields.

Table 4 Comparison of the Results of $Zn(ClO_4)_2 \cdot 6H_2O$-Catalysed Conjugate Addition of Thiols to α,β-Unsaturated Ketones with those of Reported Catalysts

Entry	Product	Cat. (mol%)	Solvent	Temp (°C)	Time	Yield (%)[b]
1	**3ba**	$InBr_3$ (10)	CH_2Cl_2[a]	r.t.	16–24 h	74[6b]
2	**3ba**	$Bi(NO_3)_3$ (15)	CH_2Cl_2[a]	r.t.	2–4 h	65[7]
3	**3ba**	$Bi(OTf)_3$ (5)	MeCN[a]	r.t.	1.5 h	72[9b]
4	**3ba**	$Zn(ClO_4)_2$ (1)	neat	r.t.	5 min	90
5	**3bb**	CdI_2 (1)	$PhCH_3$[a,b]	r.t.	12 h	74[6a]
6	**3bb**	$Zn(ClO_4)_2$ (1)	neat	r.t.	15 min	85
7	**3bc**	CdI_2 (1)	$PhCH_3$[a,b]	r.t.	12 h	48[6a]
8	**3bc**	$Zn(ClO_4)_2$ (1)	neat	r.t.	10 min	91
9	**3be**	TBAB (excess)	neat[c]	105	45 min	90[11b]
10	**3be**	$Zn(ClO_4)_2$ (1)	neat	r.t.	20 min	82
11	**3ca**	$Bi(OTf)_3$ (5)	CH_3CN	r.t.	1 h	70[9b]
12	**3ca**	TBAB (excess)	neat[c]	105	2 h	72[11b]
13	**3ca**	[pmim]Br (300 mg/mmol)	neat[d]	105	45 min	75[11c]
14	**3ca**	$Zn(ClO_4)_2$ (1)	neat	r.t.	5 min	84
15	**3ab**	$InBr_3$ (10)	CH_2Cl_2[a]	r.t.	16–24 h	78[6b]
16	**3ab**	$Zn(ClO_4)_2$ (1)	neat	r.t.	2 h	80

[a] Anhydrous solvent was used.
[b] Two equivalents of thiol were used.
[c] The molten catalyst was used as solvent.
[d] Ionic liquid was used as solvent.

A recent report suggested that the $InCl_3$-catalysed (10 mol%) conjugate addition reaction of chalcones requires anhydrous MeOH.[6c] The feasibility of carrying out the reaction of *trans*-1,3-diphenylpropenone (**1d**) with various thiols in non-anhydrous MeOH using $Zn(ClO_4)_2 \cdot 6H_2O$ as catalyst (Table 3, entries 16–20) established that the present methodology is advantageous over the reported procedure.

We have described herein a highly efficient catalyst for thia-Michael addition under solvent-free conditions at room temperature. The advantages include, (i) the use of a cheap, easy to handle and commercially available catalyst, room temperature and non-anhydrous reaction conditions, (ii) short reaction times and (iii) high yields. With increasing environmental concerns[17] the solvent-free reaction conditions should make this methodology environmentally friendly and applicable for large scale operations.

4-Phenylthio-4-phenylbutan-2-one; Typical Procedure

To a magnetically stirred mixture of *trans*-4-phenyl-3-buten-2-one (0.36g, 2.5 mmol) and thiophenol (0.30g, 2.75 mmol, 1.1 equiv) was added $Zn(ClO_4)_2 \cdot 6H_2O$ (9.3 mg, 0.025 mmol, 1 mol%). The reaction mixture was stirred at 25–30 °C for 1.5 h. After the completion of the reaction (TLC, IR), the reaction mixture was diluted with EtOAc (2 mL), adsorbed onto silica gel, charged onto a column of silica gel (60–120 mesh, 5 g), and eluted with hexane (to eliminate any disulfide formed), followed by EtOAc–hexane (1:10) to afford 4-phenylthio-4-phenyl-butan-2-one (570 mg, 89%, Table 3, entry 1) as a colourless oil.

IR (neat): 1708 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3 H), 3.04 (dd, 2 H, *J* = 2.7, 7.8 Hz), 4.70 (t, 1 H, *J* = 7.2 Hz), 7.20–7.25 (m, 10 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 30.63, 47.98, 49.44, 127.38, 127.57, 127.65, 128.43, 128.79, 132.83, 140.98, 205.46.

MS (EI): *m*/*z* = 256.

Anal. Calcd for $C_{16}H_{16}OS$: C, 74.96; H, 6.29; S, 12.51. Found: C, 74.94; H, 6.30; S, 12.49.

The remaining reactions were carried out following this general procedure. In each occasion, the spectral data (IR, NMR and MS) of known compounds were found to be identical with those reported in the literature. New spectral data are given below for representative adducts.

4-Benzylthio-4-phenylbutan-2-one (3ac)

Colourless oil.

IR (neat): 1716 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3 H), 2.91 (d, 2 H, *J* = 7.0 Hz), 3.47 (q, 2 H, J_{AB} = 13.3 Hz), 4.19 (t, 1 H, *J* = 7.2 Hz), 7.17–7.31 (m, 10 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 30.39, 35.63, 43.81, 49.89, 126.93, 127.30, 127.86, 128.36, 128.49, 128.83, 137.73, 141.43, 205.18.

MS (EI): *m*/*z* = 270.

Anal. Calcd for $C_{17}H_{18}OS$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.48; H, 6.73; S, 11.89.

3-(4-Methylphenylthio)cyclohexan-1-one (3bb)
Colourless oil.

IR (neat): 1713 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.75 (m, 2 H), 2.06–2.13 (m, 2 H), 2.20–2.37 (m, 6 H), 2.60–2.67 (m, 1 H), 3.30–3.34 (m, 1 H), 7.10 (d, 2 H, *J* = 7.8 Hz), 7.31 (d, 2 H, *J* = 7.8 Hz).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 20.93, 23.80, 30.99, 40.63, 46.23, 47.53, 128.95, 129.62, 133.69, 137.84, 208.58.

MS (EI): *m*/*z* = 220.

Anal. Calcd for $C_{13}H_{16}OS$: C, 70.87; H, 7.32; S, 14.55. Found C, 70.84; H, 7.33; S, 14.57.

4-(2-Furfurylthio)butan-2-one (3cd)
Colourless oil.

IR (neat): 1715 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 2.65–2.73 (m, 4 H), 3.71 (s, 2 H), 6.18 (s, 1 H), 6.30 (s, 1 H), 7.35 (s, 1 H).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 25.28, 28.39, 29.74, 43.09, 107.29, 110.26, 141.87, 151.33, 206.46.

MS (EI): *m*/*z* = 184.

Anal. Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56; S, 17.40. Found: C, 58.64; H, 6.58; S, 17.43.

3-Benzylthio-1,3-diphenylpropan-1-one (3dc)
White solid; mp 67–69 °C

IR (KBr): 1682 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.40–3.57 (m, 4 H), 4.45 (t, 1 H, *J* = 7.1 Hz), 7.18–7.31 (m, 8 H), 7.34–7.39 (m, 4 H), 7.46–7.51 (m, 1 H), 7.82 (d, 2 H, *J* = 7.4 Hz).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 35.78, 44.05, 45.15, 126.90, 127.23, 127.98, 128.36, 128.46, 128.85, 133.09, 136.59, 137.78, 141.67, 196.64.

MS (EI): *m*/*z* = 332.

Anal. Calcd for $C_{22}H_{20}OS$: C, 79.48; H, 6.06; S, 9.65. Found: C, 79.50; H, 6.09; S, 9.67.

3-Ethylthio-1,3-diphenylpropan-1-one (3de)
White solid; mp 59–61 °C

IR (KBr): 1678 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, 3 H, *J* = 7.3 Hz), 2.29–2.41 (m, 2 H), 3.53 (d, 2 H, *J* = 7.1 Hz), 4.58 (t, 1 H, *J* = 7.1 Hz), 7.18–7.23 (m, 1 H), 7.25–7.32 (m, 2 H), 7.40–7.45 (m, 4 H), 7.51–7.56 (m, 1 H), 7.91 (d, 2 H, *J* = 7.5 Hz).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 14.13, 25.43, 43.98, 45.35, 127.17, 127.80, 128.08, 128.49, 128.58, 133.18, 136.81, 142.22, 196.93.

MS (EI): *m*/*z* = 270.

Anal. Calcd for $C_{17}H_{18}OS$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.54; H, 6.72; S, 11.85.

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