Investigation on the Reactions of *o*-Hydroxybenzyl Alcohols with Vinyl Ethers Under Acidic and/or Thermal Conditions

Volkan Kumbaraci, Duygu Ergunes, Melike Midilli,
Seckin Begen, and Naciye Talinli*

Faculty of Science and Letters, Department of Chemistry, Istanbul Technical University,
TR-34469, Maslak, Istanbul, Turkey
*E-mail: talinlin@itu.edu.tr
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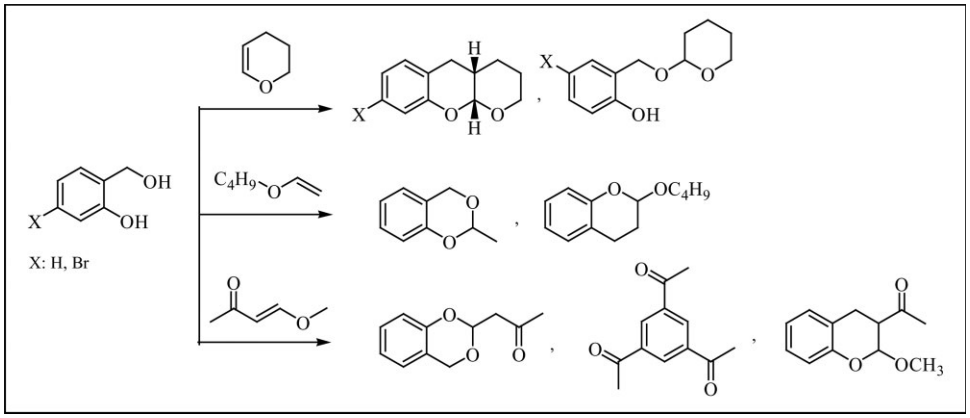

The reaction of vinyl ethers with *o*-hydroxybenzyl alcohols under different reaction conditions was investigated. The aim of this attempt was to find out whether the protection reactions or the hetero Diels–Alder reaction of quinone methide *in situ* generated from *o*-hydroxybenzyl alcohol is more likely to occur. *o*-hydroxybenzyl alcohols can give hetero Diels–Alder reactions with dihydro-2*H*-pyran at high temperatures but only when used with acid catalysts. At room temperature, even in the presence of acid catalyst, reactions yielded regular protection products. However, butyl vinyl ether and 4-methoxy-3-butenone could not give intermolecular cycloaddition reactions under the acidic conditions, because both decomposed to the new products with acids. Hetero-Diels–Alder products obtained only under thermal conditions but in low yields.

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INTRODUCTION

Protective groups play important roles in modern multistep synthetic organic chemistry and numerous publications on the selection of more suitable protecting groups for hydroxyl functions have appeared in recent years.

In our previous study, we reported selective *o*-benzylation of primary hydroxyl groups of di-and tri-hydroxyl compounds by using bis(acetylacetonato) copper as a catalyst [1].

Another well-known method for the protection of hydroxy groups is forming tetrahydropyranyl ether by reaction with 3,4-dihydro-2*H*-pyran (DHP). By using this method, diols, in which two hydroxyl groups are far away from each other can be protected in good yields. Hence, the main products are monotetrahydropyranyl ethers [2]. In these reactions, the reason for the low yield of the diprotection products is not well understood.

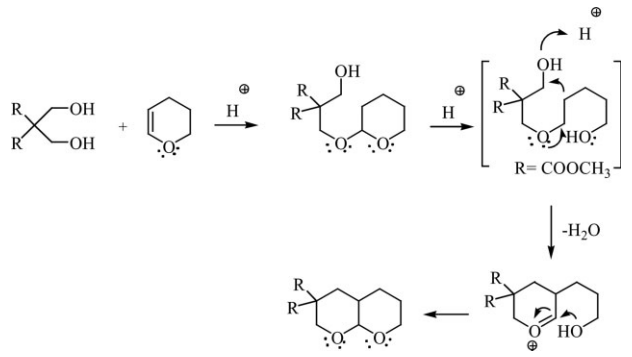
However, we have recently demonstrated that bicyclic acetals can readily be obtained with high diastereoselectivity from the reaction of 1,2- and 1,3-diols and DHP [3] (Scheme 1). In reactions carried out at 25°C using pyridine-*p*-toluene sulfonic acid (PPTS) as the catalyst, the first step is acetal formation by the addition of one of the hydroxyl groups of the diol to DHP in the usual way, the second step is ring opening of the DHP moiety and the generation of an enol ether, and the third step is water elimination and recyclization to the oxonium ion.

In particular, fused pyranobenzoxepine (**I**) was obtained from the *o*-hydroxymethylbenzyl alcohol (Fig. 1).

Formation of bicyclic acetals under catalytic conditions from aliphatic dihydroxy compounds leads us to investigate the reactions of aromatic dihydroxy compounds with DHP. We have chosen *o*-hydroxybenzyl alcohol as the diol because it has either two types of OH groups for protection reactions or it is the precursor of the quinone methide intermediate [4–6].

The aim of this study is to compare whether the protection reactions are more likely, or the hetero

Scheme 1



Diels–Alder reaction of quinone methide *in situ* generated from *o*-hydroxybenzyl alcohol is more likely to occur.

RESULTS AND DISCUSSION

Quinone methides are generally produced under thermal, photolytic, or catalytic conditions. In past years, *o*-hydroxybenzaldehydes have been preferred for generation of quinone methides under catalytic conditions [7–9]. Treatment of salicylaldehydes with 3,4-DHP in the presence of metal triflates resulted in pyrano[2,3-*b*]benzopyrans. For the reactions carried out under thermal conditions different precursors were used; while Ohwada and coworkers [10] used 4*H*-1,2-benzoxazines as precursor, Baldwin and coworkers [11] proposed a new method for *o*-quinone methide generation from *o*-methyleneacetoxy-phenols. They investigated the reactions of *o*-acetyloxymethyl phenol (2-hydroxybenzyl acetate) with dienophiles (including DHP) under thermal conditions (Scheme 2). Bray reported the generation and hetero-Diels–Alder reaction of an *o*-quinone methide using ^{i}PrMgCl under mild, anionic conditions [11]. Reactions of another precursor *o*-hydroxybenzyl alcohol and open-chain enol ethers under thermal conditions was investigated by Pochini and coworkers [12].

Under photolytic conditions *o*-hydroxybenzyl alcohol and DHP also produced benzopyranopyran derivatives [13] (Scheme 2).

However, there are no reports on the reaction of *o*-hydroxybenzyl alcohol with DHP under both catalytic and thermal conditions. Therefore, in this study, we have investigated the reaction products of DHP and *o*-hydroxybenzyl alcohol, both with acid catalysts and under thermal conditions.

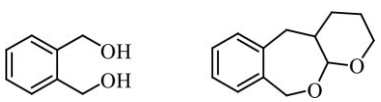
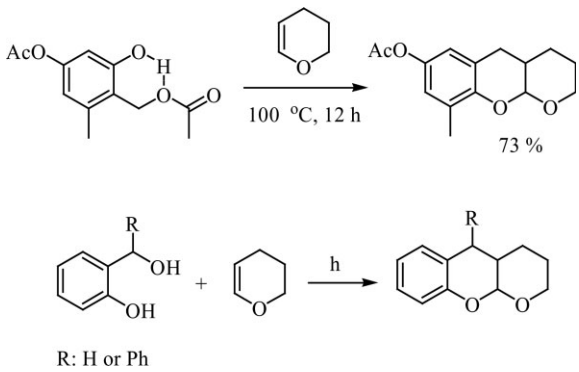


Figure 1. Reaction product of DHP and *o*-hydroxymethylbenzyl alcohol.

Scheme 2



On the basis of the concept mentioned earlier, we reacted *o*-hydroxybenzyl alcohol with DHP in the presence of PPTS at the reflux temperature of toluene. The reaction produced *cis*-fused pyrano[2,3-*b*]benzopyran (**III**) and self-reaction products of DHP (**IX**) (Scheme 3). However, the yield was lower than that of Baldwin's method. The regular mono protection product (**V**) was also obtained in low yield. Diprotection products were not detected.

The structure and the stereochemistry of compound (**III**) was elucidated by spectroscopic and chromatographic data and the results were compared with former results [7–9]. Spectroscopic data showed that the reaction was highly diastereoselective, and the coupling constant, $J = 2.6$ Hz for the bridgehead protons proved the formation of the *cis*-fused bicyclic structure.

However, when the reaction was performed in toluene without catalyst, a desired pyranobenzopyran formed in very low yield, in contrast to Baldwin's result. Mono protection product **V** was observed as main product and

Scheme 3

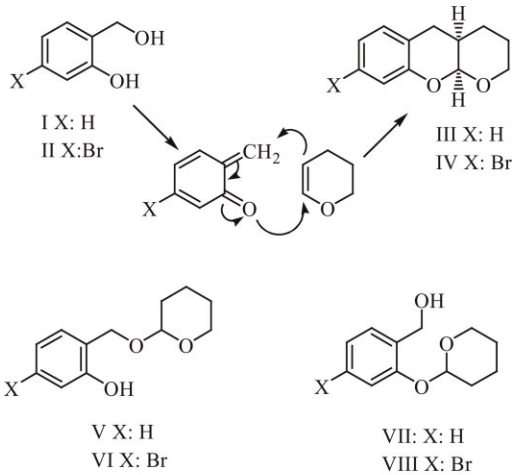


Table 1

Reaction conditions and products with yields.

Subs	Catalyst	Solvent	Temp. (°C)	Products and yields (%)[a]
I	PPTS	CH_2Cl_2	25	**V** (75) **VII** (7)[b]
I	Amb. 15	CH_2Cl_2	25	**V** (62) **VII** (10)[b]
I	PPTS	Toluene	110	**III** (35) **IX** (50) **V** (6)
I	Amb. 15	Toluene	110	**III** (15) **IX** (75)
I	–	Toluene	110	**V** (30) **III** (10)
II	PPTS	CH_2Cl_2	25	**VI** (80) **VIII** (5)[b]
II	Amb. 15	CH_2Cl_2	25	**VI** (70) **VIII** (9)[b]
II	PPTS	CH_3Cl	62	**VI** (60) **VIII** (6)[b] **IX** (10)
II	PPTS	Toluene	110	**IV** (36) **IX** (52)
II	PPTS	Toluene	110[c]	**IV** (40) **IX** (50) **VI** (4)
II	Amb. 15	Toluene	110	**IV** (15) **IX** (75)

[a] Not isolated.
[b] Reaction was performed with Dean–Stark apparatus.
[c] Yields are from GC analysis.

the rest of the reaction mixture was mainly unreacted *o*-hydroxybenzyl alcohol.

Furthermore, the reaction of 3-bromo-2-hydroxymethyl phenol with DHP under similar reaction conditions resulted in the corresponding pyranobenzopyran (**IV**).

To investigate the effect of reaction conditions on product types and their distribution, reactions were repeated at different temperatures, using different solvents and catalysts. Results of these studies are tabulated in Table 1.

The catalysts are PPTS and the strong acidic ion exchange resin Amberlyst-15. The reason for choosing Amberlyst-15 was to investigate the influence of acid structure on diastereoselectivity, but no change on stereoselectivity was observed. Increasing the reaction time did not effect the reaction yield or type of products. At room temperature, the expected protection products were obtained. As the reaction temperature was increased to 62°C self-reaction products of DHP began to form.

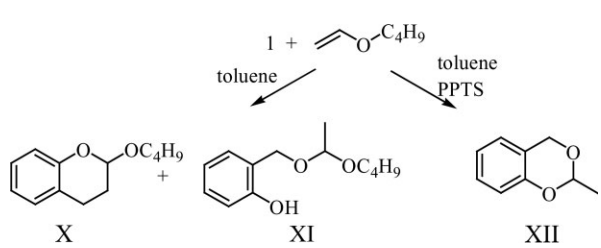
After determination of the appropriate reaction conditions for the formation of quinone methides, we worked on similar reactions of open-chain enol ethers. In this attempt, the aim was to compare the type of products with the products produced before. Butyl vinyl ether was chosen as open-chain enol ether. The reaction of butyl vinyl ether with *o*-hydroxybenzyl alcohol in toluene without catalyst resulted, mainly in two products; a corresponding 2-butoxychroman **X** (10%) and a usual addition compound **XI** (50%) (Scheme 4). The ratio of two products was determined by GC analysis of the crude product. 2-Butoxychroman has been recently produced by Ohwada and coworkers [10] under thermal conditions from 4*H*-1,2-benzoxazines, and also by Bray [11] from *o*-hydroxybenzyl acetate.

When this reaction was carried out with catalyst, none of the corresponding acetalic structures were found in the reaction mixture, instead the sole product (90%) was compound **XII** which resulted from the reaction of *o*-hydroxybenzyl alcohol and acetaldehyde produced from the decomposition of butyl vinyl ether in acidic medium. Compound **XII** was synthesized [14] before, from *o*-hydroxybenzyl alcohol and acetaldehyde dimethylacetal with 42% yield. There are several studies on the decomposition of vinyl ethers yielding acetaldehyde [15,16]. As seen in Scheme 4, similar to DHP, vinyl butyl ether afforded the desired acetalic structure with yield lower than that of the regular protection product.

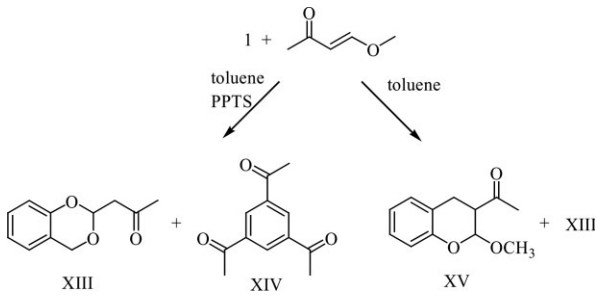
The reaction of 4-methoxy-3-butenone with *o*-hydroxybenzyl alcohol was also performed with and without catalyst. In the presence of catalyst mainly two products were obtained; compounds **XIII** (80%) and **XIV** (10%). Compound **XIII** resulted from *o*-hydroxybenzyl alcohol and 3-oxo-butanal formed *in situ* from the transformation of 4-methoxy-3-butenone [17] (Scheme 5).

Formation of compound **XIV** can be explained with the cyclization reaction of 4-methoxy-3-butenone in acidic medium as described previously [18]. When the reaction was performed without catalyst, the main product was again compound **XIII** (50%). However,

Scheme 4



Scheme 5



compound **XV** was also detected from GC-MS and ^{1}H NMR analysis with a yield of 20%. This compound is formed through the [4 + 2] cycloaddition reaction of quinone methide to 4-methoxy-3-butenone. Desktop molecular modeling calculations indicated that substituents existing in diaxial positions are more favorable structures for compound **XV**. NMR studies also supports the MM_2 calculations, because the coupling constant for acetalic and methine protons is $J = 2.8$.

These results indicated that *o*-hydroxybenzyl alcohols can give hetero Diels–Alder reactions with DHP at high temperatures but only when used with acid catalysts. At room temperature, even in the presence of acid catalyst, reactions yielded regular protection products. However, butyl vinyl ether and 4-methoxy-3-butenone could not give intermolecular cycloaddition reactions under the acidic conditions, because both decomposed to the new products with acids. Hetero-Diels–Alder products were obtained only under thermal conditions but in low yields.

EXPERIMENTAL

All general chemicals and starting materials purchased from commercial sources, except PPTS. IR spectra were recorded on a Jasco FTIR 5300 spectrometer using neat compounds as films between NaCl cells. ^{1}H and ^{13}C NMR spectra were run with Bruker 250 MHz spectrometer and reported as ppm relative to TMS. GC-MS spectra were obtained on Thermo Finnigan Trace DSQ instrument using ZB-5MS capillary column. The products were purified by column chromatography on neutral silicagel 60 (0.040–0.063 mm) from Merck, Darmstadt. Purity of compounds was proved by GC analysis (column: HP-1, 30m, 5′ 100°C, 20°C/min to 290°C, 5′ 290°C).

Preparation of PPTS. 0.15 mol of pyridine was added to 0.003 mol of *p*-toluenesulfonic acid and the mixture was stirred at room temperature for 20 min. After evaporation of pyridine, the product was crystallized from acetone.

General procedure A (with catalyst). Vinyl ether compound (2 mmol) was added dropwise to a stirred solution of I or III (1 mmol) and PPTS (0.1 mmol) in toluene (30 mL). The mixture was stirred at reflux temperature for 24 h in a Dean Stark apparatus. Then the solution was washed with half-saturated brine to remove the catalyst. After the evaporation of solvent, the crude products were purified by column chromatography using ethyl acetate/hexane as the eluent.

General procedure B (without catalyst). Vinyl ether compound (2 mmol) was added dropwise to the solution of I (1 mmol) in toluene (30 mL) and the solution was stirred for 24 h under reflux conditions. Then the solvent was evaporated and the crude product was purified by column chromatography using ethyl acetate/hexane as the eluent.

Crude products	(EtOAc/hexane)
III, IX	5/95
IV, IX	5/95
V, VII	15/85
X, XI	10/90
XII	30/70
XIII, XIV	30/70
XIII + XV	20/70/10 (ether/hexane/methanol)

3,4,4a-10a-Tetrahydro-2H,5H-pyrano[2,3-b]chromene (III). Colorless oil. ^{1}H NMR (DMSO-d_6) δ: 7.09 (d, $J = 8.4$, 1H, Ar-H_6), 7.04 (t, $J = 7.6$, 1H, Ar-H_8), 6.86 (t, $J = 7.4$, 1H, Ar-H_7), 6.78 (d, $J = 8.2$, 1H, Ar-H_9), 5.28 (d, $J = 2.4$, 1H, H_{10a}), 3.85 (td, $J = 11.9$, $J = 8.1$, 1H, H_{2ax}), 3.61 (dt, $J = 11.4$, $J = 8.2$, 1H, H_{2eq}), 2.86 (dd, $J = 16.6$, $J = 6.8$, 1H, H_{5ax}), 2.64 (dd, $J = 16.6$, $J = 5.6$, 1H, H_{5eq}), 2.08 (m, 1H, H_{4a}), 1.8–1.53 (m, 4H, 1H, $H_{3,4}$); ^{13}C NMR (DMSO-d_6) δ: 152.7, 129.5, 127.3, 120.7, 120.4, 115.9, 96.2, 62.4, 31.1, 27.8, 24.0, 22.8; ms: *m/z*: 190 (M^+), 131(58), 84 (55), 83 (100), 55 (30).

7-Bromo-3,4,4a-10a-tetrahydro-2H,5H-pyrano[2,3-b]chromene (IV). Yellowish oil. IR: 3054, 2949, 1607, 1484, 1421, 1265, 1078, 909, 756, 739, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.18 (d, $J = 8.6$, 1H, Ar-H_8), 7.14 (s,1H, Ar-H_6), 6.74 (d, $J = 8.6$, 1H, Ar-H_9), 5.31 (d, $J = 2.6$, 1H, H_{10a}), 3.98 (td, $J = 12.2$, $J = 6.1$, 1H, H_{2ax}), 3.71 (dt, $J = 11.8$, $J = 4.8$, 1H, H_{2eq}), 2.90 (dd, $J = 16.7$, $J = 5.9$, 1H, H_{5ax}), 2.60 (dd, $J = 16.7$, $J = 4.9$, 1H, H_{5eq}), 2.16 (m, 1H, 1H, H_{4a}), 1.81–1.61 (m, 4H, $H_{3,4}$); ^{13}C NMR ($CDCl_3$): δ 152.1, 131.8, 130.3, 122.1, 118.2, 112.7, 96.7, 62.6, 31.4, 28.7, 24.0, 23.4; ms: *m/z*: 270 (M + 2), 268 (M^+), 209 (15), 84 (100), 83 (85), 55 (40).

2-[(Tetrahydro-2H-pyran-2-yloxy)methyl]phenol (V). Yellowish oil. ^{1}H NMR ($CDCl_3$): δ 8.6 (broad s, 1H, OH), 7.20 (d, $J = 7.8$, 1H, Ar), 7.01–6.84 (m, 2H, Ar), 6.82 (d, $J = 8.1$, 1H, Ar), 4.90 (d, $J = 12.1$, 1H, benzylic H), 4.71 (t, $J = 2.7$, 1H, acetalic H), 4.64 (d, $J = 12.2$, 1H, benzylic H), 3.99–3.90 (m, 1H, OCH_2), 3.63–3.56 (m, 1H, OCH_2), 1.82–1.25 (m, 6H, pyran ring H); ^{13}C NMR ($CDCl_3$): δ 204.1, 152.6 128.0, 124.9, 121.3, 120.6, 116.72, 96.4, 66.5, 48.3, 31.17; ms: *m/z*: 208 (M^+), 124 (83), 108 (90), 85 (100), 77 (60).

2-Butoxychroman (X). Colorless oil. IR: 3054, 2949, 1607, 1484, 1421, 1265, 1078, 909, 756, 739, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.01–6.79 (m, 4H, Ar), 5.23 (d, $J = 2.8$, 1H, acetalic H), 3.84 (dt, $J = 9.6$, $J = 7.1$, $J = 3.6$, 1H, benzylic $H_{a(e)}$), 3.56 (dt, $J = 10.2$, $J = 6.7$, $J = 3.1$, 1H, benzylic $H_{e(a)}$), 2.95 (td, $J = 11.2$, $J = 6.2$, $J = 4.7$, 1H, OCH_2), 2.60 (dt, $J = 16.3$, $J = 3.$ 7, 1H, OCH_2), 2.16–1.87 (m, 2H,1H, ring CH_2), 1.59–1.47 (m, 2H, CH_2), 1.36–1.22 (m, 2H, CH_2), 0.86 (t, $J = 3.6$, 3H,CH_3); ^{13}C NMR ($CDCl_3$): δ 152.3, 129.2, 127.2, 122.7, 120.5,116.9, 112.7, 97.1, 67.9, 31.7, 26.6, 20.6,

19.22, 13.7; ms: *m/z*: 206.28 (M^+), 132 (72), 131 (100), 107 (38), 77 (32).

2-Methyl-4H-benzo[d][1,3]dioxine (XII). Orange liquid, IR: 3047, 2959, 2872, 1588, 1480, 1406, 1271, 1230, 1112 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.01–684 (m, 4H, Ar), 5.19 (t, $J = 5.2$, 1H, acetalic H), 5.01(d, $J = 14.6$, 1H, CH_2), 4.82 (d, $J = 14.6$, 1H, CH_2), 1.58 (d, $J = 4.9$, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 152.8, 127.6, 125.0, 120.9, 120.6, 116.7, 98.0, 66.3, 20.5; ms: *m/z*: 150.0 (M^+),105 (65), 78 (100).

1-(4H-Benzo[d][1,3]dioxin-2-yl)propan-2-one (XIII). Yellowish oil, IR: 3047, 2916, 2865, 1718, 1588, 1489, 1271, 1231, 1124, 910 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.17–6.81 (m, 4H, Ar), 5.43 (t, $J = 5.1$, 1H, acetalic H), 5.01 (d, $J = 4.6$, 1H, benzylic $H_{a(e)}$), 4.81(d, $J = 4.5$, 1H, benzylic $H_{e(a)}$), 2.97 (d, $J = 5.1$, 2H, CH_2), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 204.1, 152.61 128.02, 124.91, 121.34, 120.64, 116.72, 96.42, 66.50, 48.34, 31.17; ms: *m/z*: 192 (M^+), 174 (42), 106 (99), 78 (100).

1,3,5,-Triacetylbenzene (XIV). White crystals (mp = 163°C). ^1H NMR ($CDCl_3$): δ 8.69 (s, 3H, Ar), 2.7 (s, 9H, CH_3); EI-MS: *m/z*: 204 (M^+), 189 (100), 161 (32), 43 (53).

trans-2-Methoxy-3-acetylchroman (XV). Yellowish oil, IR: 3050, 2880, 1715, 1489, 1217, 1183, 1018, 755 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.15–6.83 (m, 4H, Ar), 5.20 (d, $J = 2.9$, 1H, acetalic H), 3.54 (s, 3H, *O*-methyl), 3.09–2.91 (m, 3H, benzylic and methine H), 2.25 (s, 3H, CH_3); ^{13}C NMR (250 MHz, $CDCl_3$): δ 205.6, 152.6, 128.91, 127.60, 124.90, 121.20, 116.90, 99.64, 58.2, 49.78, 30.75, 24.78; ms: *m/z*: 206 (M^+), 174 (24), 132 (26), 130 (100), 43 (24). *Anal*. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.62, H, 6.95.

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