APPLIED ORGANOMETALLIC CHEMISTRY
*Appl. Organometal. Chem.* 2003; **17**: 851–855
Main Group Metal Compounds
Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/aoc.531

# Practical generation of 3,5-dimethoxybenzyllithium: application to the synthesis of 5-substituted-resorcinols

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Received 11 July 2003; Revised 16 July 2003; Accepted 19 July 2003

**Reductive lithiation of 3,5-dimethoxybenzyl methyl ether was successfully performed with lithium wire and a catalytic amount of naphthalene in dry tetrahydrofuran at −15 °C, leading to the quantitative generation of 3,5-dimethoxybenzyllithium. This organometallic compound, which can be stored for at least 24 h, was trapped with a variety of different electrophiles, including, besides aldehydes, non-functionalized and functionalized alkyl halides and an epoxide. Accordingly, it is a useful intermediate in the synthesis of 5-substituted natural and non-natural resorcinols. Copyright © 2003 John Wiley & Sons, Ltd.**

**KEYWORDS:** carbanions; ethers; reduction; resorcinols

## INTRODUCTION

5-Alkyl- and 5-alkenyl-substituted resorcinols are an important class of natural and synthetic products endowed with significant biological and pharmacological properties.[1,2] Furthermore, they are useful intermediates in the synthesis of cannabinoids, the psychotomimetically active constituents of marijuana.[3–5] Accordingly, there is a continuous search for new approaches to their synthesis.[4,6–9] Recently, Yus and co-workers[6] reported on the generation of 3,5-dimethoxybenzyllithium as a useful intermediate in the synthesis of such compounds.

However, the proposed approach to the generation of this organolithium derivative, i.e. naphthalene-catalysed reductive lithiation of 3,5-dimethoxybenzyl trimethylsilyl ether under Barbier-type reaction conditions, practically limits to carbonyl derivatives the number of electrophiles that can be added to the carbanionic intermediate.

We have already reported that reductive cleavage of benzyl alkyl ether is a useful approach to the generation of benzyllithium derivatives[10] and wish now to describe the practical application of this procedure to the generation of stable solutions of 3,5-dimethoxybenzyllithium, which can be efficiently trapped with a wide array of different electrophiles, including aldehydes, functionalized and non-functionalized alkyl halides, and epoxides. As an improvement of our previous results, reductive lithiations were successfully carried out employing lithium wire instead of the more reactive, but less easy to handle, lithium powder or lithium dispersion in mineral oil; for a laboratory-scale preparation of lithium dispersion in silicone oil and lithium powder, see Yus *et al*.[11]

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## RESULTS AND DISCUSSION

3,5-Dimethoxybenzyl methyl ether (**1**) was prepared by reaction of the corresponding, commercially available, benzyl alcohol with NaH in dry tetrahydrofuran (THF) followed by addition of $CH_3I$.

Reductive cleavages of ether **1** were carried out under argon with an excess of lithium wire (10 equivalents) in the presence of a catalytic amount of naphthalene (10 mol%) in THF at −15 °C; the results are reported in Table 1 (Scheme 1). Under these conditions, 3,5-dimethoxytoluene (**3a**) was recovered quantitatively after aqueous work up (Table 1, entry 1).

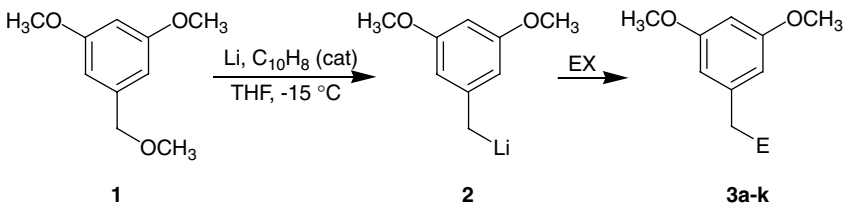
Intermediate, quantitative formation of 3,5-dimethoxybenzyllithium (**2**) was evidenced by quenching the reaction mixture with $D_2O$; accordingly, $^1H$ NMR analysis of crude 3,5-dimethoxy-$\alpha$-deuterobenzyl methyl ether (**3b**) showed 92% incorporation of deuterium in the benzylic position (Table 1, entry 2).

To check the stability under the reported reaction conditions of intermediate **2**, the reaction mixture was stirred

**Table 1.** Reductive lithiation of ether **1** and reaction with electrophiles

| Entry | Electrophile, EX[a] | Product | | |
|---|---|---|---|---|
| | | No. | E | Yield (%)[b] |
| 1 | $H_2O$ | **3a** | H | >95[c] |
| 2 | $D_2O$ | **3b** | D | >92[c] |
| 3 | $D_2O$[d] | **3b** | D | 87[c] |
| 4 | $C_4H_9Br$ | **3c** | $C_4H_9$ | 76 |
| 5 | $C_{12}H_{25}Br$ | **3d** | $C_{12}H_{25}$ | 73 |
| 6 | $PhCH_2Cl$ | **3e** | $PhCH_2$ | 56 |
| 7 | $BrC_{12}H_{24}Br$[e] | **3f** | $ArC_{13}H_{26}$[f] | 60 |
| 8 | $Br(CH_2)_{10}OH$[e] | **3g** | $(CH_2)_{10}OH$ | 62 |
| 9 | $BrCH_2CH(OCH_2)_2$ | **3h** | $CH_2CH(OCH_2)_2$ | 55 |
| 10 | 1-Butene oxide[g] | **3i** | $CH_2CH(OH)C_2H_5$ | 55 |
| 11 | PhCHO | **3j** | PhCHOH | 70 |
| 12 | 4-$(CH_3O)C_6H_4CHO$ | **3k** | 4-$(CH_3O)C_6H_4CHOH$ | 80 |

[a] All reductions were run at −15 °C for 5 h, then quenched with 1.1 equivalents of EX, unless indicated otherwise.
[b] Isolated yield, unless indicated otherwise.
[c] As determined by $^1H$ NMR spectroscopy.
[d] $D_2O$ was added after 24 h stirring at −15 °C.
[e] 0.5 equivalents of EX; isolated yield was calculated accordingly.
[f] Ar = 3,5-$(CH_3O)_2C_6H_3$.
[g] 2.2 equivalents of EX.




**Scheme 1.** Reductive lithiation of ether **1** and reaction with electrophiles. **3a**, E = H; **3b**, E = D; **3c**, E = $C_4H_9$; **3d**, E = $C_{12}H_{25}$; **3e**, E = $PhCH_2$; **3f**, $(CH_2)_{13}Ar$; **3g**, E = $(CH_2)_{10}OH$; **3h**, E = $CH_2CH(OCH_2)_2$; **3i**, E = $CH_2CHOHC_2H_5$;**3j**, E = $C_6H_5CHOH$; **3k**, E = 4-$(CH_3O)C_6H_4CHOH$. Ar = 3,5-$(CH_3O)_2C_6H_3$..

at −15 °C for 24 h, before $D_2O$ quenching and work up. Under the new conditions, $^1H$ NMR analysis of crude **3b** showed 87% incorporation of deuterium in the benzylic position (Table 1, entry 3).

The relatively high stability of intermediate **2** allows its trapping with different electrophiles, which can be added to the reaction mixture once the reductive cleavage procedure is over.

According to this procedure, organolithium **2** was reacted with 1.1 equivalents of BuBr affording olivetol dimethyl ether (**3c**) in 76% isolated yield (Table 1, entry 4). This result compares well with an analogous alkylation experiment conducted after reduction of the substrate with lithium dispersion in mineral oil.[10]

As an extension of this procedure, intermediate **2** was successfully reacted with other primary alkyl halides; indeed, quenching the reduction mixture with dodecylbromide or benzylchloride afforded the dimethyl ether of, respectively, grevillol (**3d**) or dihydropinosilvin (**3e**) in satisfactory yields (Table 1, entries 5 and 6).

Conversion of compounds **3c–e** into the corresponding, naturally occurring, lipidic resorcinols is already known.[6]

Furthermore, reaction with 0.5 equivalents of 1,12-dibromododecane afforded the tetramethyl ether **3f** (Table 1, entry 7); the latter compound, according to a literature procedure, can be converted into 1,3-dihydroxy-5-[14′-(3″,5″-dihydroxyphenyl)tetradecyl]-benzene, a natural lipidic resorcinol able to cleave DNA in the presence of $Cu^{2+}$.[12,13]

As an approach to the synthesis of resorcinols bearing an additional functional group on the alkyl chain, suitable for further elaboration, we investigated the reactivity of intermediate **2** with functionalized alkyl halides and with an epoxide. Accordingly, reaction with 10-bromodecanol (0.5 equivalents), 2-bromoethyl-1,3-dioxolane (1.1 equivalents), and 1-butene oxide (2.2 equivalents) led to the recovery of the dimethyl ethers of functionalized resorcinols **3g**, **3h** and **3i** respectively in satisfactory yields (Table 1, entries 8–10).

Finally, synthetically useful yields were obtained when reacting benzyllithium **2** with aromatic aldehydes; indeed, quenching the reduction mixture with benzaldehyde or

4-methoxybenzaldehyde afforded benzylic alcohols **3j** and **3k** (Table 1, entries 11 and 12). Conversion of these alcohols into the corresponding, biologically active, stilbenic resorcinols, namely pinosilvine and resveratrol, was described recently.[6]

## CONCLUSIONS

We have reported that naphthalene-catalysed reductive lithiation of 3,5-dimethoxybenzyl methyl ether allows the generation of stable solutions of 3,5-dimethoxybenzyllithium.

This organometallic intermediate was efficently trapped with different electrophiles. Reaction with alkyl halides afforded useful intermediates in the synthesis of naturally occurring lipidic resorcinols (**3c–f**), and reaction with functionalized alkyl halides, or with an epoxide, afforded the dimethyl ethers of 5-substituted resorcinols bearing an additional functionality on the alkyl chain (**3g–i**), suitable for further elaboration. These latter derivatives appear particularly useful, owing to interest in the synthesis of non-natural analogues of tetrahydrocannabinoids bearing functionalized alkyl chains in the resorcinolic moiety.[4,8,9]

Finally, our procedure led to the addition of 3,5-dimethoxybenzyllithium to aldehydes in good yields (alcohols **3j** and **3k**), thus improving the results previously reported under Barbier-type reaction conditions.[6]

## EXPERIMENTAL

### General

Boiling and melting points are uncorrected; the air-bath temperature on bulb-to-bulb distillation is given as the boiling point. Starting materials were of the highest commercial quality and were purified by distillation immediately prior to use. Lithium wire, 99.9% purity, was 3.2 mm diameter, and $D_2O$ was 99.8% isotopic purity. THF was distilled from Na–K alloy under dinitrogen immediately prior to use. $^1$H NMR spectra were recorded at 300 MHz and $^{13}$C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $SiMe_4$ as internal standard. Deuterium incorporation was calculated by monitoring the $^1$H NMR spectra of crude reaction mixtures, and by comparing the integration of the signal corresponding to protons in the arylmethyl position with that of known signals. Flash chromatography were performed on Merck silica gel 60 (40–63 μm), and thin-layer chromatography analyses were performed on Macherey–Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

### 3,5-Dimethoxybenzyl methyl ether (1)

NaH (1.96 g of a 60% dispersion in mineral oil, 49 mmol) was placed under dry dinitrogen in a 250 ml two-necked flask equipped with reflux condenser and magnetic stirrer, washed with dry THF (3 × 10 ml), and suspended in dry THF (70 ml). The mixture was chilled to 0 °C and a solution of 3,5-dimethoxybenzyl alcohol (6.9 g, 41 mmol) dissolved in THF (15 ml) was added dropwise. The resulting mixture was stirred for 4 h at room temperature. To this reaction mixture, chilled to 0 °C, a solution of $CH_3I$ (7.0 g, 3.1 ml, 49 mmol) dissolved in 10 ml of THF was slowly added. After stirring overnight at room temperature, the mixture was quenched by slow dropwise addition of $H_2O$ (20 ml), and the resulting mixture was extracted with $Et_2O$ (3 × 20 ml). The organic phase was washed with brine (10 ml), dried ($Na_2SO_4$) and evaporated. The crude product was purified by distillation, to afford 3,5-dimethoxybenzyl methyl ether (6.4 g, 35 mmol, 85% yield), which was characterized as follows.

Colourless oil; b.p. 178 °C/30 mmHg (lit.[14] 138 °C/12 mmHg). $^1$H NMR: $\delta$ 3.38 (3H, s, $CH_3O$), 3.79 (6H, s, 2 × $CH_3O$), 4.41 (2H, s, $CH_2$), 6.39 (1H, t, $J$ = 2.4 Hz, ArH), 6.50 (2H, d, $J$ = 2.4 Hz, 2 × ArH).

### Reductive cleavage of ether 1, and reaction with electrophiles. general procedure

150 mg of Li wire (22 mg atom, 10 equivalents) were placed under argon in a 50 ml two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in THF (5 ml). A catalytic amount of naphthalene (28 mg, 0.22 mmol, 10 mol%) was added to the suspended metal, each metal piece was cut into two or three smaller pieces with a spatula, and the mixture stirred until a dark green colour appeared. The mixture was chilled to −15 °C and a solution of **1** (0.4 g, 2.2 mmol), dissolved in 5 mL of dry THF, was added dropwise. The mixture was stirred at −15 °C for 5 h, and a solution of the appropriate electrophile (0.5–2.2 equivalents, see Table) in THF (2 ml) was added slowly. After stirring for 30 min, the mixture was quenched by slow dropwise addition of $H_2O$ (10 ml, *caution*), the cold bath removed, and the resulting mixture extracted with $Et_2O$ (3 × 10 ml). The organic phase was washed with brine (10 ml), dried ($Na_2SO_4$) and the solvent evaporated.

$D_2O$ quenching was performed by slow dropwise addition of 0.75 ml of the electrophile dissolved in dry THF (2 ml), followed by aqueous work-up as described above.

Quenching with $BrC_{12}H_{24}Br$ (0.5 equivalents) was accomplished with an inverse addition technique, followed by aqueous work-up as described above.

Quenching with 1-butene oxide (2.2 equivalents) was performed at −30 °C, followed by aqueous work-up as described above.

Crude products were purified and characterized as described below.

### 3,5-Dimethoxytoluene (3a)

Purified by flash chromatography (petroleum ether/AcOEt, 9.5 : 0.5), colourless oil; $R_f$ (petroleum ether/AcOEt, 9.5 : 0.5) 0.44; b.p. 85 °C/10 mmHg (lit.[15] 95 °C/30 mmHg). $^1$H NMR: $\delta$ 2.31 (3H, s, $CH_3$), 3.77 (6H, s, 2 × $CH_3O$), 6.28 (1H, t, $J$ = 2.4

Hz, ArH), 6.34 (2H, d, $J = 2.4$ Hz, 2 × ArH). $^{13}$C NMR: $\delta$ 21.8, 55.2, 97.6, 107.1, 140.2, 160.8.

### α-Deutero-3,5-dimethoxytoluene (3b)

Purified by flash chromatography (petroleum ether/AcOEt, 9.5 : 0.5), colourless oil; $R_f$ (petroleum ether/AcOEt, 9.5 : 0.5) 0.44; b.p. 85 °C/10 mmHg. $^1$H NMR: $\delta$ 2.26–2.30 (2H, m, $CH_2D$), 3.77 (6H, s, 2 × $CH_3O$), 6.28 (1H, t, $J = 2.4$ Hz, ArH), 6.34 (2H, d, $J = 2.4$ Hz, 2 × ArH).

### 1,3-Dimethoxy-5-pentylbenzene (3c)

Purified by flash chromatography (petroleum ether/AcOEt, 9 : 1), colourless oil; $R_f = 0.52$ (petroleum ether/AcOEt, 9 : 1); b.p. 131 °C/2 mmHg (lit.[15] b.p. 98 °C/0.3 mmHg). $^1$H NMR: $\delta$ 0.90 (3H, t, $J = 6.9$ Hz, $CH_3$), 1.24–1.38 (4H, m, 2 × $CH_2$), 1.52–1.63 (2H, m, $CH_2$), 2.54 (2H, t, $J = 7.8$ Hz, $CH_2Ar$), 3.78 (6H, s, 2 × $CH_3O$), 6.30 (1H, t, $J = 2.1$ Hz, ArH), 6.35 (2H, d, $J = 2.1$ Hz, 2 × ArH).

### 1,3-Dimethoxy-5-tridecylbenzene (3d)

Purified by recrystallization (EtOH), white solid; m.p. 43 °C (lit.[15] m.p. 37–39 °C). $^1$H NMR: $\delta$ 0.88 (3H, t, $J = 7.2$ Hz, $CH_3$), 1.23–1.40 (20H, m, 10 × $CH_2$), 1.53–1.62 (2H, m, $CH_2$), 2.54 (2H, t, $J = 7.5$ Hz, $CH_2Ar$), 3.78 (6H, s, 2 × $CH_3O$), 6.29 (1H, t, $J = 2.4$ Hz, ArH), 6.34 (2H, d, $J = 2.4$ Hz, 2 × ArH). $^{13}$C NMR: $\delta$ 14.1, 22.7, 29.3, 29.5, 29.6, 29.7, 31.3, 31.9, 36.3, 55.2, 97.5, 106.4, 145.4, 160.6.

### 3,5-Dimethoxy-5-(2′-phenylethyl)benzene (3e)

Purified by fractional distillation, colourless oil; b.p. 130 °C/1 mmHg (lit.[16] 86–88 °C/0.1 mmHg); $R_f = 0.41$ (petroleum ether/AcOEt, 9 : 1). $^1$H NMR: $\delta$ 2.81–2.95 (m, 4H 2 × $CH_2$), 3.76 (6H, s, 2 × $CH_3O$), 6.31 (1H, t, $J = 2.1$ Hz, ArH), 6.34 (2H, d, $J = 2.1$ Hz, 2 × ArH), 7.15–7.22 (3H, m, 3 × ArH), 7.25–7.31 (2H, m, 2 × ArH). $^{13}$C NMR: $\delta$ 37.7, 38.2, 55.2, 97.9, 106.5, 125.9, 128.3, 128.4, 141.7, 144.2, 160.7.

### 1,3-Dimethoxy-5-[14′-(3″,5″-dimethoxyphenyl)tetradecyl]-benzene (3f)

Purified by flash chromatography (petroleum ether/AcOEt, 9.5 : 0.5), white solid; $R_f = 0.30$ (petroleum ether/AcOEt, 9.5 : 0.5); m.p. 65 °C (lit.[17] m.p. 64.5–65 °C, petroleum ether). $^1$H NMR: $\delta$ 1.24–1.29 (20H, m, 10 × $CH_2$), 1.56–1.61 (4H, m, 2 × $CH_2$), 2.54 (4H, t, $J = 7.8$ Hz, 2 × $CH_2Ar$), 3.78 (12H, s, 4 × $CH_3O$), 6.30 (2H, t, $J = 2.4$ Hz, 2 × ArH), 6.34 (4H, d, $J = 2.4$ Hz, 4 × ArH). $^{13}$C NMR: $\delta$ 29.3, 29.5, 29.6, 29.7 (2C), 31.3, 36.3, 55.2, 97.5, 106.4, 145.4, 160.6.

### 11-(3′,5′-Dimethoxyphenyl)undecan-1-ol (3g)

Purified by flash chromatography (petroleum ether/AcOEt, 8 : 5), white solid; $R_f = 0.39$ (petroleum ether/AcOEt, 8 : 5); m.p. 40 °C. Anal. Found: C, 73.78; H 10.57; $C_{19}H_{32}O_3$ requires: C, 73.97; H, 10.48%. IR (neat) 3375 cm$^{-1}$. $^1$H NMR: $\delta$ 1.18–1.46 (17H, m, 8 × $CH_2$, OH), 1.49–1.52 (2H, m, $CH_2$), 2.47 (2H, t, $J = 7.2$ Hz, $CH_2Ar$), 3.57 (2H, t, $J = 7.2$ Hz, $CH_2O$), 3.71 (6H, s, 2 × $CH_3O$), 6.23 (1H, t, $J = 2.2$ Hz, ArH), 6.28 (2H, d, $J = 2.2$ Hz, 2 × ArH). $^{13}$C NMR: $\delta$ 25.7, 29.3, 29.4, 29.5, 29.5 (2C), 29.7, 31.3, 32.8, 36.3, 55.2, 63.1, 97.5, 106.4, 145.4, 160.6.

### 2-[2′-(3″,5″-Dimethoxyphenyl)ethyl]-[1,3]dioxolane (3h)

Purified by flash chromatography (petroleum ether/AcOEt/$Et_3N$, 8 : 2 : 0.5), light yellow oil; $R_f = 0.30$ (petroleum ether/AcOEt/$Et_3N$, 8 : 2 : 0.5). Anal. Found: C, 65.37; H 7.84; $C_{13}H_{18}O_4$ requires: C, 65.52; H, 7.63%. $^1$H NMR: $\delta$ 1.94–2.01 (2H, m, $CH_2$), 2.66–2.72 (2H, m, $CH_2Ar$), 3.77 (6H, s, 2 × $CH_3O$), 3.85–3.89 (2H, m, $CH_2O$), 3.96–4.02 (2H, m, $CH_2O$), 4.89 (1H, t, $J = 4.8$ Hz, CH), 6.30 (1H, t, $J = 2.0$ Hz, ArH), 6.37 (2H, d, $J = 2.0$ Hz, 2 × ArH). $^{13}$C NMR: $\delta$ 30.4, 35.3, 55.2, 64.9, 97.9, 103.7, 106.4, 144.0, 160.7.

### 1-(3′,5′-Dimethoxyphenyl)pentan-3-ol (3i)

Purified by flash chromatography (petroleum ether/AcOEt, 7 : 3), light yellow oil; $R_f = 0.37$ (petroleum ether/AcOEt, 7 : 3); b.p. 170 °C/1 mmHg. IR (neat) 3390 cm$^{-1}$. Anal. Found: C, 69.34; H 9.32; $C_{13}H_{20}O_3$ requires: C, 69.60; H, 9.00%. $^1$H NMR: $\delta$ 0.94 (3H, t, $J = 7.5$ Hz, $CH_3$), 1.40–1.58 (2H, m, $CH_2$), 1.65–1.86 (3H, m, $CH_2$, OH), 2.61 (1H, ddd, $J = 13.8$, 9.6, 6.6 Hz, CH), 2.75 (1H, ddd, $J = 13.8$, 9.6, 6.0 Hz, CH), 3.52–3.61 (1H, m, CHO), 3.78 (6H, s, 2 × $CH_3O$), 6.30 (1H, t, $J = 2.1$ Hz, ArH), 6.37 (2H, d, $J = 2.1$ Hz, 2 × ArH). $^{13}$C NMR: $\delta$ 9.8, 30.2, 32.4, 38.3, 55.2, 72.5, 97.7, 106.4, 144.6, 160.7.

### 2-(3′,5′-Dimethoxyphenyl)-1-phenylethanol (3j)

Purified by flash chromatography (petroleum ether/AcOEt, 7 : 3), light yellow oil; $R_f = 0.39$ (petroleum ether/AcOEt, 7 : 3). IR (neat) 3445 cm$^{-1}$. $^1$H NMR: $\delta$ 2.02 (1H, br s, OH), 2.87–3.03 (2H, m, $CH_2Ar$), 3.76 (6H, m, 2 × $CH_3O$), 4.87–4.93 (1H, m, CHO), 6.36 (3H, s, 3 × ArH), 7.26–7.39 (5H, m, 5 × ArH). $^{13}$C NMR: $\delta$ 46.4, 55.2, 75.0, 98.6, 107.3, 125.9, 127.6, 128.4, 140.2, 143.7, 160.8 ($^1$H and $^{13}$C NMR spectra are in agreement with literature data[6,7]).

### 2-(3″,5″-Dimethoxyphenyl)-1-(4′-methoxyphenyl)ethanol (3k)

Purified by flash chromatography (petroleum ether/AcOEt, 6 : 4), light yellow oil; $R_f = 0.35$ (petroleum ether/AcOEt, 6 : 4). IR (neat) 3487 cm$^{-1}$. $^1$H NMR: $\delta$ 1.87 (1H, br s, OH), 2.86–3.01 (2H, m, $CH_2Ar$), 3.77 (6H, s, 2 × $CH_3O$), 3.82 (3H, s, $CH_3O$), 4.86 (1H, dd, $J = 8.1$, 5.1 Hz, CHO), 6.36 (3H, s, 3 × ArH), 6.87–6.92 (2H, m, 2 × ArH), 7.28–7.33 (2H, m, 2 × ArH). $^{13}$C NMR: $\delta$ 46.2, 55.1, 55.2, 74.6, 98.5, 107.3, 113.6, 127.1, 135.9, 140.4, 158.9, 160.7 ($^1$H and $^{13}$C NMR spectra are in agreement with literature data[6,7]).

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