# Preparation of 2,9-Dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione by Sodium Azide-Promoted Cyclodimerization of *o*-Acylthiophenacyl Chloride

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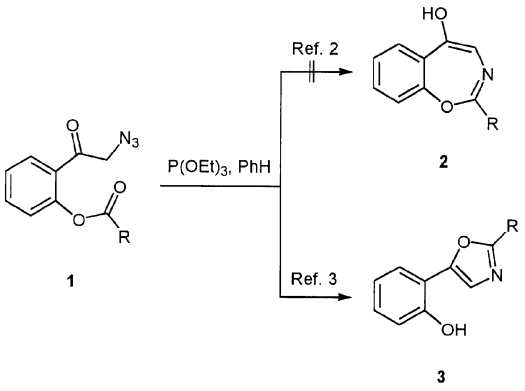
The reaction of *o*-acylthiophenacyl chloride **5a** with one equivalent of sodium azide in aqueous acetone at -10~ -5 °C gave 2,9-dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione **7** (10%), acyclic dimer **8** (64%) and trimer **9** (8%). Dimer **8** and trimer **9** were converted readily to **7** under the similar conditions at room temperature in yields of 72% and 53%, respectively. Also, one pot synthesis of **7** (64%, 45%) from the reaction of **5a** or **5b** with two equivalents of sodium azide at room temperature was very successful.

## Introduction

The aza-Wittig reaction, in particular its intramolecular version, has drawn considerable attention recently because of its high potential for the synthesis of nitrogen heterocycles.[1] We reported[2] the synthesis of 5-hydroxy-1,3-benzoxazepines based on the Staudinger reaction followed by an intramolecular aza-Wittig reaction of *o*-acyloxyphenacyl azides **1**. However, Peet *et al.*[3] have reinvestigated this procedure and found that it produced, instead, a 5-(2-hydroxyphenyl)-1,3-oxazoles **3** (Scheme 1). In this connection, we were interested in the synthesis of their thio analogs, 5-(2-mercaptophenyl)-1,3-oxazoles in a similar manner. We now report the unexpected synthesis of 10-membered diketo dithiaorthocyclophane, 2,9-dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione **7** by the reaction of *o*-acylthiophenacyl chlorides **5** with sodium azide.

Dithiacyclophanes are usually prepared by the reaction of a dithiol with a dihalide under basic conditions[4] and the chemistry of dithiacyclophanes has been widely investigated in recent times. A significant driving force for this effort is the application of ligands for coordination chemistry.[5] This phenomenon opens the possibility of applying these thioethers in the extraction of heavy metals[6] resulting in interesting perspectives for environmental and medicinal chemistry.




**Scheme 1**

## Results and Discussion

The starting *o*-acylthiophenacyl chlorides **5** were obtained by the Friedel-Crafts acylation of the known *S*-acyl-*p*-thiocresol (**4**)[7] with chloroacetyl chloride by the conventional way as shown in Scheme 2. Treatment of **5a** with one equivalent of sodium azide in aqueous acetone at -10 ~ -5 °C did not give the *o*-acylthiophenacyl azide **6**, but led to the formation of unexpected diketo dithiaorthocyclophane **7** (10%), acyclic dimer **8** (64%) and trimer **9** (8%) which were separated by column chromatography. In contrast, the benzoyl-substituted phenacyl chloride **5b** under the similar condition resulted only in the recovery of starting material. However, at room temperature, the reaction proceeded smoothly to give only the cyclodimerization product, 2,9-dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione (**7**) in 45% yield. This demonstrated clearly that diketo dithiaorthocyclophane **7** could be prepared from acyclic dimer **8** under similar conditions. Therefore, the acyclic dimer **8** was converted readily to the 10-membered diketo dithiaorthocyclophane **7** using one equivalent of sodium azide at room temperature in 72% yield. When acyclic trimer **9** was treated with sodium azide under the similar conditions, cyclic trimer **10** was not produced at all, instead cyclodimerization product **7** (53%) was obtained. Also, one pot synthesis of **7** (64%) from the reaction of **5a** with two equivalents of sodium azide in aqueous acetone at room temperature was very successful. Presumably the role of sodium azide was deacylation of thioester.

Because of its high reactivity as a deacylation-cyclodimerization agent, several bases such as tetrabutylammonium fluoride, potassium hydroxide, sodium carbonate, and *N*,*N*-dimethylaminopyridine (DMAP) were next employed in this reaction, however, no better results were obtained than sodium azide (Table 1).

Further we have investigated sodium azide-promoted cyclodimerization of oxa analogs **11**[8] and **12** under the similar condition. The only product obtained was the *o*-hydroxyphenacyl azide **13** in 76% and 78% yields, respectively. No cyclodimerization product was produced. When warmed with sodium hydroxide in aqueous tetrahydrofuran, 2-hydroxy-5-

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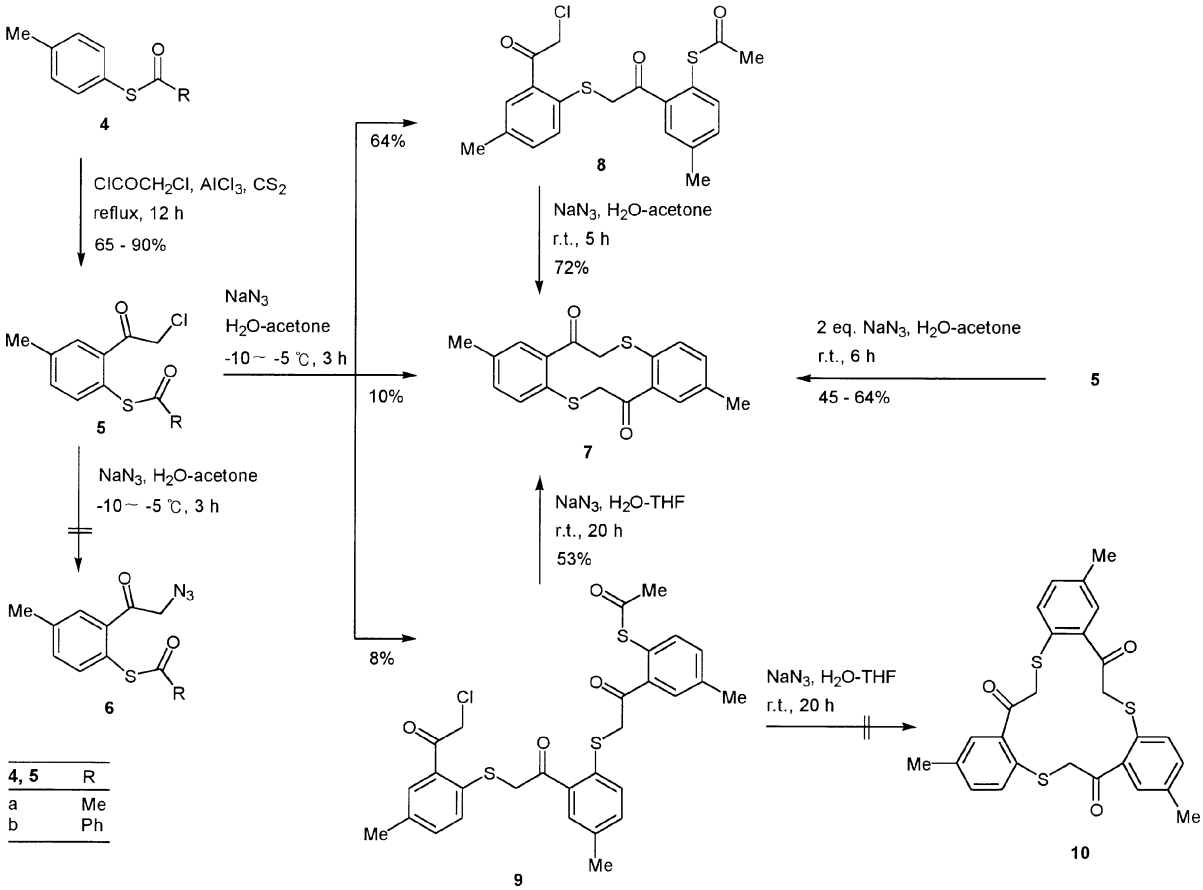



**Scheme 2**

**Table 1**. 2,9-Dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione (**7**) Synthesis

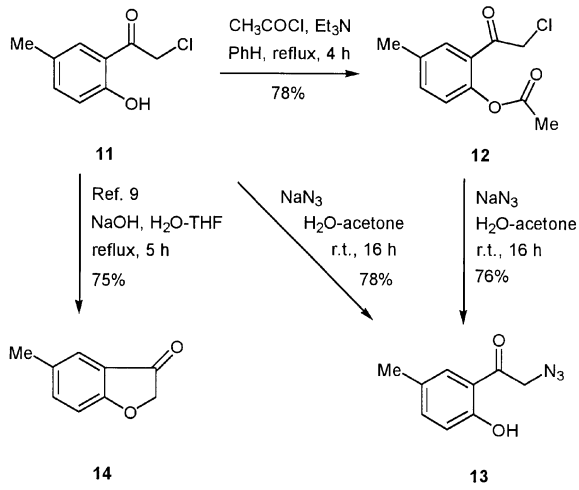
| Entry | Base[a] | Reaction Solvent | Reaction Time (h)[b] | Yield (%) |
|---|---|---|---|---|
| 1 | $NaN_3$ | acetone/$H_2O$ (6/4) | 6[c] | 64 |
| 2 | $Bu_4NF$ | THF | 6 | 48 |
| 3 | KOH | THF/$H_2O$ (6/4) | 2 | 15 |
| 4 | $Na_2CO_3$ | THF/$H_2O$ (6/4) | 24 | 13 |
| 5 | DMAP | THF | 24 | 9 |

[a]Two equivalents of base were used. [b]Reflux temperature. [c]Room temperature.

ethylphenacyl chloride (**11**) yielded the known 5-methyl-3(2*H*)-benzofuranone (**14**)[9] (Scheme 3).

Structural elucidation of **7** was accomplished on the basis of spectral data and microanalyses. The $^1H$ NMR spectra showed a peak at $\delta = 3.95$ for the methylene protons, and the methyl protons resonated in the $\delta = 2.42$. The aromatic multiplets ranged from $\delta = 6.92$ to 7.41. The $^{13}C$ NMR exhibited peaks at $\delta = 20.4$ ($CH_3$) and 44.0 ($CH_2$) in addition to the six aromatic peaks as well as peak at $\delta = 199.0$ for the carbonyl carbon. Compound **7** exhibited strong band at $\delta = 1666$ $cm^{-1}$ (C=O) in its infrared spectrum, and showed an intense molecular ion (m/z = 328) peak in the mass spectrum.

In summary, a novel and convenient route to dibenzo-annelated 10-membered diketo dithiaorthocyclophane **7** from the




**Scheme 3**

-acylthiophenacyl chloride **5** with sodium azide has been developed.

## Experimental Section

All reagents and solvents were reagent grade or were purified by standard methods before use. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was sup-

plied by E. Merck. Analytical thin layer chromatography (tlc) was performed on silica gel with fluorescent indicator coated on aluminium sheets. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Thermoquest EA 1110 element analyzer. Compounds gave C, H, N, S analysis ± 0.39%. The mass spectra were recorded on a Hewlett Packard model 5890 II spectrometer with an electron beem energy of 70 eV. Infrared spectra were recorded on a Nicolet Magna 760 FTIR spectrometer. The $^1$H and $^{13}$C NMR spectra were measured on a Gemini 300 spectrometer. All chemical shifts are reported in parts per million ($\delta$) relative to tetramethylsilane.

*S*-Acetyl-*p*-thiocresol (**4a**)[7], *S*-benzoyl-*p*-thiocresol (**4b**)[7] and 2-hydroxy-5-methylphenacyl chloride (**11**)[8] were prepared following the literature procedures.

***o*-Acetylthiophenacyl Chloride 5a**. To a solution of *S*-acetyl-*p*-thiocresol (**4a**, 10.0 g, 60 mmol) in $CS_2$ (60 mL) was added chloroacetyl chloride (5.71 mL, 72 mmol). The mixture was stirred vigorously while $AlCl_3$ (28.0 g, 210 mmol) was added in portions over a period of 20 min. at r.t. The mixture was refluxed for 12 h and heating and stirring was stopped, and allowed to stand for 1 h, during which time it was separated into two layers. The upper layer was decanted and the viscous reddish brown lower layer was poured cautiously into crushed ice (100 g) and conc. HCl (10 mL) was added and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined extracts were dried ($MgSO_4$), concentrated to dryness, and crystallized from petroleum ether to give product **5a**; yield 13.1 g (90%); mp 80-82. $^1$H NMR ($CDCl_3$): $\delta$ = 2.44 (s, 3 H, $CH_3$), 2.54 (s, 3 H, $CH_3$), 4.62 (s, 2 H, $CH_2$), 7.33 7.65 (m, 3 $H_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 193.1, 193.0, 140.6, 137.8, 135.1, 134.3, 132.9, 125.4, 47.7, 30.0, 20.9; Anal. found for $C_{11}H_{11}ClO_2S$ C, 54.04; H, 4.69; S, 13.45 calcd: C, 54.43; H, 4.57; S, 13.21.

***o*-Benzoylthiophenacyl Chloride 5b**. The same procedure as described in formation of **5a** was repeated using *S*-benzoyl-*p*-thiocresol (**4b**, 13.7 g, 60 mmol) to afford product **5b**; yield 9.46 g (65%); mp 112-114. $^1$H NMR ($CDCl_3$): $\delta$ = 2.58 (s, 3H, $CH_3$), 4.65 (s, 2H, $CH_2$), 7.38-8.03 (m, 8$H_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 193.2, 189.5, 141.0, 138.6, 136.1, 135.3, 135.1, 133.9, 133.1, 128.8, 127.4, 125.0, 47.8, 21.2; Anal. found for $C_{16}H_{13}ClO_2S$ C, 62.78; H, 4.23; S, 10.22 calcd: C, 63.05; H, 4.30; S, 10.52.

**2,9-Dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione (7), Dimer 8 and Trimer 9**. To a stirred solution of *o*-acetylthiophenacyl chloride (**5a**, 2.91 g, 12 mmol) in acetone (36 mL) was added dropwise a solution of $NaN_3$ (0.78 g, 12 mmol) in $H_2O$ (24 mL) at -10 ~ -5 °C. The mixture was stirred for 3 h at ambient temperature whereupon acetone was removed under reduced pressure. The residual material was extracted with $CH_2Cl_2$ (2 × 30 mL), dried over $MgSO_4$, concentrated to dryness, and chromatographed (silica gel; EtOAc-hexane, 1 : 6) to give **7**, **8** and **9** in the order of elution. **7**; yield: 0.19 g (10%); mp 179-181 °C. IR (KBr): $\nu$ = 1666 cm$^{-1}$ (CO); $^1$H NMR ($CDCl_3$): $\delta$ = 2.42 (s, 6 H, $CH_3$), 3.95 (s, 4H, $CH_2$), 6.91 (d, $J$ = 1.7 Hz, 1$H_{arom}$), 7.08 (d, $J$ = 8.0 Hz, 1$H_{arom}$), 7.40 (dd, $J$ = 1.7, $J$ = 8.0 Hz, 1$H_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 199.0, 138.6, 137.9, 136.1, 135.8, 132.4, 130.6, 44.4, 20.4; MS: m/z (%) = 328 ($M^+$, 61), 165 (20), 163 (30), 151 (100), 137 (20), 135 (20), 121 (23), 91 (18), 77 (11); Anal. found for $C_{20}H_{19}ClO_3S_2$ C, 58.89; H, 4.86; S, 16.05 calcd: C, 59.03; H, 4.71; S, 15.76. **8**; yield: 1.5 g (64%); mp 105-107 °C. $^1$H NMR ($CDCl_3$): $\delta$ = 2.39 (s, 3H, $CH_3$), 2.44 (s, 3H, $CH_3$), 2.47 (s, 3H, $CH_3$), 4.18 (s, 2H, $CH_2$), 4.58 (s, 2H, $CH_2$), 7.18-7.59 (m, 6$H_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 196.3, 193.5 (two), 140.6, 138.5, 137.4, 136.6, 135.1, 134.5, 132.9 (two), 131.8, 131.0, 125.2, 47.8, 43.4, 30.1, 21.0 (two), 20.8; MS: m/z (%) = 406 ($M^+$, 9), 193 (100), 151 (44), 121 (18), 91 (8), 77 (8); Anal. found for $C_{29}H_{27}ClO_4S_3$ C, 60.61; H, 5.00; S, 16.81 calcd: C, 60.98; H, 4.77; S, 16.84. **9;** yield: 0.18 g (8%); mp 114-116 °C. $^1$H NMR ($CDCl_3$): $\delta$ = 2.33 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$), 2.43 (s, 3H, $CH_3$), 2.46 (s, 3H, $CH_3$), 4.16 (s, 4H, two $CH_2$), 4.58 (s, 2H, $CH_2$), 7.14-7.61 (m, 9$H_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 196.6, 196.4, 193.6, 193.5, 140.7, 138.4, 137.5, 136.6, 136.4, 135.2, 134.6, 134.4, 134.2, 132.9, 132.8, 132.1, 131.7, 131.3 (two), 130.9 (two), 125.3, 47.9, 43.4, 30.2, 30.1, 21.1, 20.9, 20.7; Anal. found for $C_{18}H_{16}O_2S_2$ C, 65.99; H, 4.92; S, 19.86 calcd: C, 65.82; H, 4.91; S, 19.52.

**2,9-Dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione (7) from Dimer 8**. To a stirred solution of dimer (**8**, 0.81 g, 2 mmol) in acetone (20 mL) was added dropwise a solution of $NaN_3$ (0.14 g, 2.2 mmol) in $H_2O$ (12 mL) at r.t. The mixture was stirred for 5 h at r · t., whereupon acetone was removed under reduced pressure. The residual material was extracted with $CH_2Cl_2$ (2 × 10 mL), dried over $MgSO_4$, concentrated to dryness, and crystallized from ether to give product **7**; yield 0.47 g (72%).

**2,9-Dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione (7) from Trimer 9**. To a stirred solution of trimer (**9**, 1.14 g, 2 mmol) in THF (20 mL) was added dropwise a solution of $NaN_3$ (0.14 g, 2.2 mmol) in $H_2O$ (12 mL) at r.t. The mixture was stirred for 20 h at r · t. whereupon THF was removed under reduced pressure. The residual material was extracted with $CH_2Cl_2$ (2 × 10 mL), dried over $MgSO_4$, concentrated to dryness, and chromatographed (silica gel; EtOAc-hexane, 1 : 8) to give product **7**; yield 0.35 g (53%).

**One-Pot Synthesis of 2,9-Dimethyl-6*H*,13*H*-dibenzo[*d*,*i*][1,6]dithiecin-7,14-dione (7) from 5; General Procedure**. Method A: To a stirred solution of *o*-acylthiophenacyl chloride **5a** or **5b** (8 mmol) in acetone (24 mL) was added dropwise a solution of $NaN_3$ (1.04 g, 16 mmol) in $H_2O$ (16 mL) at r · t. The mixture was stirred for 6 h at r · t., whereupon acetone was removed under reduced pressure. The residual material was extracted with $CH_2Cl_2$ (2 × 30 mL), dried over $MgSO_4$, concentrated to dryness, and chromatographed (silica gel; EtOAc-hexane, 1 : 8) to give **7**; yield 1.68 g (64%) or 1.18 g (45%), respectively.

Method B: The reaction was performed using the same procedure as described in Method A but with reduced amounts (1/4). Other bases and reaction solvent such as $Bu_4NF$, KOH, $Na_2CO_3$, DMAP and THF are used instead of $NaN_3$ and acetone. After work up as described in Method A,

the product **7** was obtained by column chromatography (silica gel; EtOAc-hexane, 1 : 8) (Table 1).

**2-Acetoxy-5-methylphenacyl Chloride (12).** To a stirred solution of 2-hydroxy-5-methylphenacyl chloride (**11**, 1.48 g, 8 mmol) in benzene (20 mL) was added acetyl chloride (0.85 mL, 12 mmol) and $Et_3N$ (1.66 mL, 12 mmol). The mixture was refluxed for 4 h and washed with water (10 mL), dried ($MgSO_4$), concentrated to dryness, and crystallized from petroleum ether to give product **12**; yield 1.41 g (78%); mp 49-51 °C. $^1$H NMR ($CDCl_3$): $\delta$ = 2.35 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 4.62 (s, 2H, $CH_2$), 7.06-7.57 (m, 3H$_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 190.7, 169.3, 147.0, 136.0, 134.9, 130.3, 127.5, 123.5, 48.1, 21.1, 20.7; Anal. found for $C_{11}H_{11}ClO_3$ C, 58.21; H, 4.76 calcd: C, 58.29; H, 4.89.

**2-Hydroxy-5-methylphenacyl Azide (13).** To a stirred solution of 2-hydroxy-5-methylphenacyl chloride (**11**, 0.50 g, 2.7 mmol) or 2-acetoxy-5-methylphenacyl chloride (**12**, 0.61 g, 2.7 mmol) in acetone (12 mL) was added dropwise a solution of $NaN_3$ (0.35 g, 5.4 mmol) in $H_2O$ (8 mL) at r · t. The mixture was stirred for 16 h at r · t. whereupon acetone was removed under reduced pressure. The residual material was extracted with $CH_2Cl_2$ (2 × 10 mL), dried over $MgSO_4$, concentrated to dryness, and chromatographed (silica gel, EtOAc-hexane, 1 : 5) to give product **13**; yield: 0.39 g (78%) and 0.40 g (76%), respectively; mp 46-48 °C. IR (KBr): $\nu$ = 3433 (OH), 2116 ($N_3$), 1642 (CO); $^1$H NMR ($CDCl_3$): $\delta$ = 2.31 (s, 3H, $CH_3$), 4.58 (s, 2H, $CH_2$), 6.94 (d, $J$ = 8.1 Hz, 1 H$_{arom}$), 7.26-7.36 (m, 2H$_{arom}$), 11.49 (s, 1H, OH); $^{13}$C NMR ($CDCl_3$): $\delta$ = 198.3, 160.3, 138.3, 128.6, 128.2, 118.6, 116.9, 54.1, 20.3; Anal. found for $C_9H_9O_2N_3$ C, 56.30; H, 4.59; N, 22.18 calcd: C, 56.54; H, 4.74; N, 21.98.

**5-Methyl-3(2*H*)-benzofuranone (14).** To a stirred solution of 2-hydroxy-5-methylphenacyl chloride (**11**, 0.50 g, 2.7 mmol) in THF (15 mL) was added a solution of NaOH (0.11 g, 2.7 mmol) in $H_2O$ (2 mL). The mixture was stirred for 5 h at reflux temperature whereupon THF was removed under reduced pressure. The residual material was extracted with $CH_2Cl_2$ (2 × 20 mL), dried over $MgSO_4$, concentrated to dryness, and chromatographed (silica gel, EtOAc-hexane, 1 : 10) to give the known product **14**; yield: 0.28 g (75%); m.p 45-47 °C (Lit.[9] 51-52 °C). IR (KBr): $\nu$ = 1720 cm$^{-1}$ (CO); $^1$H NMR ($CDCl_3$): $\delta$ = 2.35 (s, 3H, $CH_3$), 4.60 (s, 2H, $CH_2$), 7.01-7.43 (m, 3H$_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ = 199.9, 172.4, 139.1, 131.5, 123.3, 121.0, 113.1, 74.9, 20.5; MS: m/z (%) = 148 ($M^+$, 90), 119 (100), 91 (71).

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