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One-Pot Three-component Synthesis of 3-hydroxy-5,5-dimethyl-2-[phenyl(phenylthio)methyl]cyclohex-2-enone Derivatives under Ultrasound

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Abstract: 3-hydroxy-5,5-dimethyl-2-[phenyl(phenylthio)methyl]cyclohex-2-enone is synthesized via one-pot three-component reactions of aromatic aldehyde, substituted thiophenol and 5,5-dimethyl-1,3-cyclohexanedione catalyzed by *p*-dodecylbenzene sulfonic acid （DBSA）under ultrasound. Under ultrasound irradiation the yields are much higher (sometimes substantially, by almost double) and the reaction time decreases substantially, the reaction conditions are milder. This method provides several advantages such as environment friendliness, high yields and simple work-up procedure and the protocol provides a novel alternative for the synthesis of thioether.

Key word: 3-Hydroxy-5,5-dimethyl-2-[phenyl(phenylthio)methyl]cyclohex-2-enone; DBSA; Ultrasound; Three-component reaction; 5,5-Dimethyl-1,3-cyclohexanedione

1. Introduction

The preparation of sulfur-containing molecules has been a long-term mainstay of organic synthesis because of their broad application to organic and medicinal chemistry [1]. Thioether compounds are important biologically active compounds, as a sulfur atom can significantly increase affinity of receptor and ligand [2], which possess antibacterial activities [3], antifungal and anticancer activities [4]. They are also used in anthelmintic and/or nematocidal [5]. The sulfide compounds can be synthesised in many ways. The Ullmann S-arylation reaction involves the formation of biaryl sulfides from the corresponding aryl sulfides and aryl halides in the presence of a metal catalyst [6-8]. The thio-Michael addition reaction has emerged as one tool

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for C-S bond formation [9]. Conjugate addition of sulfur-centered nucleophiles to α,β-unsaturated carbonyls such as chalcones serves as a powerful synthetic method in the area of sulfur chemistry [10]. Mustafa et al [11] reported that a series of novel chalcone derivatives containing thiophenol were prepared by addition of thiophenol to chalcones in the presence of a catalytic amount of *t*-BuOK in solvent free conditions.

Multicomponent reactions (MCRs) are chemical transformations in which three or more different starting materials combine together via a one-pot procedure to give a final complex product. Recently, MCRs have received great attention from organic chemists，which offers important advantages over conventional linear-type synthesis，such as high atom economy, low cost, reduction in overall reaction time and operational simplicity [12-16]. Such reactions have emerged as powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry for their facileness and efficiency as well as their economy and ecology in organic synthesis [17]. They have proven to be fast, convergent, atom efficient reactions and avoiding complicated purifications [14]. MCRs have emerged as a valuable tool in the synthesis of drug libraries because they have significant advantages over conventional reaction strategies to generate biologically active scaffolds with significant structural diversity [18].

Consequently, designing novel MCRs for the synthesis of diverse drug-like molecules has been the focus of many researchers [19]. Ultrasound has increasingly been used in organic synthesis in the last three decades. Ultrasonic irradiation leads to the acceleration of numerous catalytic reactions in homogeneous and heterogeneous systems. A large number of organic reactions can be carried out in higher yield, shorter reaction time and mild condition under ultrasound [20, 21]. Zou et al reported a green and convenient approach to the synthesis of dihydropyrano[2,3-c]pyrazoles via four-component reaction of aromatic aldehydes, hydrazine, ethyl acetoacetate and malononitrile in water under ultrasound irradiation[22] which not only afforded good yield but also higher reaction rates (88% yield in 30 min). Hu et al[23] also reported one-pot three-component procedure for synthesis of novel dispirooxindolecyclo[pyrrolo[1,2-c]thiazole-6,5'-thiazolidine] derivatives without any

catalysts under ultrasonic condition which has some advantages, such as mild reaction conditions, good yield and short reaction times. Three-components condensation reaction of 8-hydroxy quinoline, aldehydes and sulfone derivative has been developed for the synthesis of 4H-pyrano [3,2-h]quinoline derivatives containing sulfone moiety under ultrasonic irradiation via utilization of *p*-TsOH as a catalyst[24]. Fuchs et al [25] reported a way of one pot synthesis thioethers by condensation of thiophenol, 1,3-diketone and 2-naphthaldehyde. It is used silica gel as catalyst and dichloromethane as solvent for 5d at room temperature. Continue our work of DBSA as catalyst under ultrasoud irradiation in the three-component reaction [26], thiophenol, benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione were empolyed in the reaction and a series of novel thioether compounds 3-hydroxy-5,5-dimethyl-2-[phenyl(phenylthio)methyl]cyclohex-2-enone（**Scheme 1**）were obtained.

Scheme 1.

2. Results and discussion

To optimize the reaction conditions, the multicomponent reaction of 4-fluorothiophenol, benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione catalyzed by DBSA was selected as the model under ultrasound irradiation.

The effect of molar ratio of reactants on reaction was investigated. As shown in Table 1, when molar ratio of 4-fluorothiophenol, benzaldehyde and 5,5-dimethyl-1,3-cyclo-hexanedione was 1:1.2:1.2, the best yield of 3-hydroxy-5,5-dimethyl-2-[phenyl(phenylthio)methyl]cyclohex-2-enone was achieved (82%, Table 1, Entry 7), but the reaction time increased to 120 min. Considering the amount of benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione both were increased by 20% while the yield was only increased by 3%, so the molar ratio of thiopnenol, benzaldehyde, and 5,5-dimethyl-1,3-cyclohex-anedione was chosen to 1:1:1.

As shown in Table 1, the temperature had a significant effect on the yield and reaction time. When the reaction was carried out at 25 ^{o}C, it took 100 min and gave

79% yield (Entry 2), but when the temperature was 40 °C, the reaction time was shortened to 80 min and the yield was 60 % (Entry 9). When the temperature was 50 °C, the reaction time was shortened to 80 min and the yield was 55% (Entry 10). The reaction yield at 25 °C was better than at 40 °C or 50 °C. So the following experiment was carried out at 25 °C.

The effect of irradiation frequency on the reaction was also examined. When the frequency was 40 kHz, the yield of **4a** (79%) (Table 1, Entry 2) was better than that with 25 kHz irradiation within 140 min (60%, Table 1, Entry 8). The result showed that 40 kHz was the appropriate frequency for this reaction.

The effect of the amount of DBSA on the reaction was observed. When the amounts of DBSA were 5 mol%, 7.5 mol% and 10 mol%, the yields of **4a** were 60% (Entry 4), 68% (Entry 3) and 79% (Entry 2), respectively. Increasing the amount of DBSA to 15 mol% (Entry 1), either the yield or the reaction time compared with 10 mol% (Entry 2) did not improve. In the absence of DBSA, three-component reaction was carried out in 45% yield with 150 min under ultrasound (Entry 5). While in the presence of DBSA (10 mol%) with the same temperature and the molar ratio of reactants, **4a** was obtained in 79% yield (Entry 2) with 100 min under ultrasound and 63% yield with 180 min without ultrasound (Entry 11). It is shown that the amount of catalyst and ultrasound has a significant effect on the reaction.

From the above results, the optimum reaction conditions were chosen: thiophenol (**1**, 1 mmol), aromatic aldehyde (**2**, 1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**3**, 1 mmol), DBSA (10 mol%), water (2 mL), ultrasound frequency 40 kHz, and reaction temperature 25 °C. Using this reaction system, a series of experiments for the syntheses of **4a**-**w** were carried out, and the results are summarized in Table 2.

As shown in Table 2, this condensation was carried out with good yields catalyzed by DBSA in aqueous media under ultrasound irradiation. A comparative analysis for the obtained data leads to interesting conclusions concerning the influence of ultrasound and without ultrasound in synthesis. It could be noticed that ultrasound enhanced a remarkable acceleration for reactions, the reactions time

decreasing and the yield increasing. Cavitation is the origin of sonochemistry. Liquids irradiated with ultrasound can produce bubbles. Under the proper conditions these bubbles undergo a violent collapse, which generates localized “hot spot” with a transient high temperature and pressures, inducing molecular fragmentation, and highly reactive species are locally produced. In the heterogeneous reactions involving immiscible liquid, the reaction between these species can only occur in the interfacial region between the liquids. Cavitation can also increase the rate of mass transfer between two phases, and induce the reaction rapidly [27].

Table 1

Table 2

4v was not found in the reaction, the phenomenon maybe described thiophenol steric effect. When the substituent is an amino group or a hydroxyl group (Entry **4s**, **4t** and **4u**), the desired product was not generated, maybe it is that thiophenol and amino or hydroxy group form intramolecular hydrogen bonds, which hindered thiol nucleophilic reaction. When dimedone was instead of 1,3-cyclohexanedione, the expected product **4x** appeared, but the yield (20%) was much lower than the corresponding dimedone. If dimedone was instead of other 1,3-cyclic dicarbonyl derivatives such as barbituric acid, the expected product was not obtained. When aliphatic thiole such as octanethiol was in place of the substituted thiophenol in the reaction, the object product did not appeare, in that the nucleophile of octanethiol was weaker than substituted thiophenol.

When aromatic aldehyde was p-nitrobenzaldehyde containing strong withdrawing group, the target product was absent. It is maybe the carbocation intermediate (Scheme 2, 9) was unstable.

Scheme 2 to afford a probable explanation of the multicomponent reaction of aromatic aldehyde, thiophenol and 5,5-dimethyl-1,3-cyclohexane-dione. Firstly, aldol condensation reaction is occurred between aromatic aldehyde and 5,5-dimethyl-1,3-cyclohexanedione, forming β-hydroxyl ketone (Scheme 2, 7). Hydroxy combines a hydrogen ion and loss of water molecules to form a carbocation

(Scheme 2, 9). Thiophenol attacking carbocation occur nucleophilic addition, and the excess of hydrogen ions of the sulfur is stripped to form the target product (Scheme 2, 4).

Scheme 2

3. Conclusions

In conclusion, we have found an efficient procedure for the synthesis of 3-hydroxy-5,5-dimethyl-2-[phenyl(phenylthio)methyl]cyclohex-2-enone derivatives *via* one-pot three-component reaction of aromatic aldehyde, thiophenol and 5,5-dimethyl-1,3-cyclohexanedione catalyzed by DBSA in water under ultrasound irradiation and the protocol provides a novel alternative for the synthesis of thioether.

4. Experimental

4.1 Apparatus and analysis

Melting points were determined with a SGW X-4 microscopic melting point apparatus (Shanghai Precision & Scientific Instrument Co., Ltd, P. R. China) in open capillaries and were uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE III 600 (600 MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. HRMS spectra were determined on a Bruker apex ultra 7.0 T Fourier transform mass spectrometer. The IR spectra were recorded as potassium bromide disk on IR Prestige-21/FTIR-8400S. Sonication was performed in Shanghai Branson-BUG40-06 and Branson-BUG25-06 ultrasonic cleaner (Shanghai Branson, 40 kHz and 25 kHz, 250W).

4.2 General procedure

A 25 mL Erlenmeyer flask was charged with thiophenol (**1**, 1 mmol), aromatic aldehydes (**2**, 1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**3**, 1 mmol), DBSA (0.1 mmol), and water (2 mL). The reaction flask was located in the ultrasonic bath, where the surface of reactants is slightly lower than the level of the water, and irradiated at 25 ^{o}C (bath temperature, the temperature inside the reactor was also 25 ^{o}C) for the period of time (the reaction was monitored by TLC). The reaction temperature was

controlled by addition or removal of water from ultrasonic bath. After completion of the reaction, the mixture was diluted with ice water (10 mL), the solid was filtered, washed with cold water and dried to give crude product, which was further purified by column chromatography on silica gel (200-300 mesh) eluted with petroleum ether (b.p. 60-90^{o}C) or a mixture of petroleum ether and ethyl acetate (petroleum ether/ethyl acetate = 4/1, V/V). The authenticity of compounds was established by ^{1}H NMR, ^{13}C NMR, IR and HRMS.

4.2.1 Compound **4a**

2-[(4-Fluoro-phenylsulfanyl)-phenyl-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-en one; white, acicular crystal solid; m.p.126-127^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ9.34 (s, 1H, -OH), 7.45-7.42 (m, 4H, Ar-H), 7.36-7.34 (m, 2H, Ar-H), 7.30-7.29 (m, 1H, Ar-H), 7.03-7.00 (m , 2H, Ar-H), 6.14 (s, 1H, -CH-), 2.47 (d, J = 17.5 Hz, 1H, -CH_2-CO-), 2.24 (d, J = 17.5 Hz, 1H, -CH_2-CO-), 2.20 (d, J = 16.1 Hz, 1H, -CH_2-C=C-), 2.08 (d, J = 16.1 Hz, 1H, -CH_2-C=C-), 1.03 (s, 3H, -CH_3), 0.79 (s, 3H, -CH_3).^{13}C NMR (150 MHz, $CDCl_3$) δ196.78, 173.24, 163.45, 161.80, 137.52, 133.62, 133.56, 130.13, 128.88, 128.17, 128.15, 127.91, 116.37, 116.22, 111.53, 50.257, 47.13, 43.43, 31.73, 28.35, 27.58. HRMS (ESI^{+}) $[M+H]^{+}$: calcd. for $C_{21}H_{22}FO_2S$: 357.1279, Found: 357.1267. IR (KBr) (ν_{max}, cm^{-1}): 3074, 2954, 1652, 1636.

4.2.2 Compound **4b**

3-Hydroxy-2-[(4-methoxy-phenylsulfanyl)-phenyl-methyl]-5,5-dimethyl-cyclohex-2-enone, faint yellow solid, m.p.120-121^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.60 (s, 1H, -OH), 7.44 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.41 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.34 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.30-7.27 (m, 1H, Ar-H), 6.85 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.04 (s, 1H, -CH-), 3.80 (s, 3H, -OCH_3), 2.47 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.27 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.17 (d, *J* = 16.1 Hz, 1H, -CH_2-C=C-), 2.06 (d, *J* = 16.1 Hz, 1H, -CH_2-C=C-), 1.02 (s, 3H, -CH_3), 0.79 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.70, 173.10, 160.00, 137.89, 135.90, 133.91, 128.79, 127.93, 123.35, 114.76, 111.56, 55.34, 50.34, 47.86, 43.49, 31.72, 28.31, 27.70. HRMS (ESI^{+}) $[M+H]^{+}$: calcd. for $C_{22}H_{25}O_3S$: 369.1479. Found: 369.1446. IR (KBr) (ν_{max}, cm^{-1}): 3066, 2953, 1652, 1635.

4.2.3 Compound **4c**

2-[(2-Fluoro-phenylsulfanyl)-phenyl-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-en one, white solid; m.p.128-129°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.21 (s, 1H, -OH), 7.46 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.43 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, Ar-H), 7.31-7.27 (m, 2H, Ar-H), 7.11-7.07 (m, 2H, Ar-H), 6.26 (s, 1H, -CH-), 2.46 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.24 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.20 (d, *J* = 16.1 Hz, 1H, $-CH_2$-C=C-), 2.09 (d, *J* = 16.1 Hz, 1H, $-CH_2$-C=C-), 1.03 (s, 3H, $-CH_3$), 0.77 (s, 3H, $-CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.47, 173.34, 162.50, 160.86, 137.49, 137.45, 133.39, 131.30, 129.99, 129.93, 128.44, 128.29, 127.98, 126.78, 124.67, 124.65, 116.06, 115.90, 111.47, 50.32, 45.61, 43.46, 31.67, 28.38, 27.52. HRMS (ESI^+)$[M+H]^+$: calcd. for $C_{21}H_{22}FO_2S$: 357.1279. Found: 357.1252. IR (KBr) (ν_{max}, cm^{-1}):3058, 2953, 1652, 1636.

4.2.4 Compound **4d**

3-Hydroxy-5,5-dimethyl-2-(phenyl-o-tolylsulfanyl-methyl)-cyclohex-2-enone,faint yellow solid; m.p.123-124°C, ^{1}H NMR (600 MHz, CDCl3) δ9.45 (s, 1H, -OH), 7.47 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.38-7.35 (m, 2H, Ar-H), 7.30 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.21-7.12 (m, 3H, Ar-H), 6.19 (s, 1H, -CH-), 2.48 (s, 3H, $-CH_3$), 2.46 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.25 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.21 (d, *J* = 16.1 Hz, 1H, $-CH_2$-C=C-), 2.12 (d, *J* = 16.1 Hz, 1H, $-CH_2$-C=C-), 1.03 (s, 3H, $-CH_3$), 0.82(s, 3H, $-CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.71, 173.46, 138.64, 137.82, 132.26, 130.62, 130.41, 128.87, 128.00, 127.87, 127.56, 126.56, 111.44, 50.35, 44.62, 43.44, 31.76, 28.42, 27.69, 20.28. HRMS (ESI^+) $[M+H]^+$: calcd. for $C_{22}H_{25}O_2S$: 353.1529; Found: 353.1542. IR (KBr) (ν_{max}, cm^{-1}): 3078, 2947, 1652, 1635.

4.2.5 Compound **4e**

3-Hydroxy-5,5-dimethyl-2-(phenyl-p-tolylsulfanyl-methyl)-cyclohex-2-enone, faint yellow solid; m.p. 125-126°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.65(s, 1H, -OH), 7.48 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.35-7.33 (m, 3H, Ar-H), 7.31-7.28 (m, 2H, Ar-H), 7.12 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.13 (s, 1H, -CH-), 2.45 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.33 (s, 3H, $-CH_3$), 2.26 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.20 (d, *J* = 16.1 Hz, 1H, $-CH_2$-C=C-), 2.10 (d, *J* = 16.1 Hz, 1H, $-CH_2$-C=C-), 1.02 (s, 3H, $-CH_3$), 0.79 (s, 3H,

-CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.78, 173.25, 138.00, 131.34, 129.88, 128.78, 128.24, 127.99, 126.82, 125.86, 111.89, 50.32, 46.93, 43.50, 31.75, 28.40, 27.61, 21.13. HRMS(ESI$^+$) $[M+H]^+$: calcd. for $C_{22}H_{25}O_2S$: 353.1529; Found: 353.1524. IR (KBr) (ν_{max}, cm^{-1}): 3071, 2947, 1652, 1635.

4.2.6 Compound **4f**

2-[(2,4-Dimethyl-phenylsulfanyl)-phenyl-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-enone, faint yellow solid; m.p. 138-139^{o}C, ^{1}H NMR (600 MHz, CDCl3) δ9.55 (s, 1H, -OH), 7.46 (d, J = 7.5 Hz, 2H, Ar-H), 7.36 (t, J = 7.5 Hz, 2H, Ar-H), 7.30 -7.28(m, 1H, Ar-H), 7.21 (d, J = 7.9 Hz, 1H, Ar-H), 7.04 (s, 1H, Ar-H), 6.93 (d, J = 7.9 Hz, 1H, Ar-H), 6.12 (s, 1H, -CH-), 2.48 (s, 3H, -CH_3), 2.45 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.29 (s, 3H, -CH_3), 2.26 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.20 (d, J = 16.1 Hz, 1H, -CH_2-C=C-), 2.11 (d, J = 16.1 Hz, 1H, -CH_2-C=C-), 1.04 (s, 3H, -CH_3), 0.83 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.65, 173.32, 139.09, 138.08, 137.89, 131.54, 131.29, 128.81, 128.53, 127.97, 127.76, 127.25, 111.57, 50.35, 45.09, 43.45, 31.74, 28.35, 27.75, 20.97, 20.25. HRMS (ESI$^+$) $[M+H]^+$: calcd. for $C_{23}H_{27}O_2S$: 367.1686; Found: 367.1689. IR (KBr) (ν_{max}, cm^{-1}): 3077, 2955, 1652, 1635.

4.2.7 Compound **4g**

2-[(2,4-Dichloro-phenylsulfanyl)-phenyl-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-enone faint yellow solid; m.p. 155-156^{o}C, ^{1}H NMR (600 MHz, CDCl3) δ8.98 (s, 1H, -OH), 7.47 (d, J = 2.0 Hz, 1H, Ar-H), 7.43 (d, J = 7.5 Hz, 2H, Ar-H), 7.38-7.35 (m, 3H, Ar-H), 7.31 (d, J = 7.3 Hz, 1H, Ar-H), 7.25 (dd, J = 8.4, 2.0 Hz, 1H, Ar-H), 6.19 (s, 1H, -CH-), 2.47 (d, J = 17.5 Hz, 1H, -CH_2-CO-), 2.29(d, J = 17.5 Hz, 1H, -CH_2-CO-), 2.25 (d, 2H J = 16.1 Hz, 1H, -CH_2-C=C-), 2.16 (d, J = 16.1 Hz, 1H, -CH_2-C=C-), 1.05 (s, 3H, -CH_3), 0.86 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.73, 173.23, 137.04, 133.62, 133.09, 131.96, 130.83, 129.66, 129.00, 128.12, 127.90, 126.78, 111.44, 50.23, 46.18, 43.42, 31.75, 28.38, 27.53. HRMS (ESI$^+$) $[M+H]^+$: calcd. for $C_{21}H_{21}Cl_2O_2S$: 407.0594; Found: 407.0621, IR(KBr) (ν_{max}, cm^{-1}): 3063, 2947, 1652, 1635.

4.2.8 Compound **4h**

2-[(2-Chloro-phenyl)-(2,4-dimethyl-phenylsulfanyl)-methyl]-3-hydroxy-5,5-dimethyl

-cyclohex-2-enone, faint yellow solid; m.p. 152-153°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ10.11 (s, 1H, -OH), 7.45 -7.41 (m, 2H, Ar-H), 7.25 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.24-7.23 (m, 1H, Ar-H), 7.04 (s, 1H, Ar-H), 6.95 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.36 (s, 1H, -CH-), 2.49 (s, 3H, $-CH_3$), 2.48 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.34 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.29 (s, 3H, $-CH_3$), 2.20 (d, J = 16.1 Hz, 1H, $-CH_2$-C=C-), 2.11 (d, J = 16.1 Hz, 1H, $-CH_2$-C=C-), 1.03 (s, 3H, $-CH_3$), 0.88 (s, 3H, $-CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.43, 173.76, 139.14, 137.90, 135.74, 134.57, 131.59, 130.77, 130.43, 129.17, 128.99, 128.35, 127.35, 127.19, 111.19, 50.37, 43.65, 43.37, 31.75, 28.21, 27.88, 20.95, 20.37. HRMS(ESI$^+$) $[M+H]^+$: calcd. for $C_{23}H_{26}ClO_2S$: 401.1297; Found: 401.1335. IR(KBr) (ν_{max}, cm^{-1}): 3077, 2947, 1652, 1635.

4.2.9 Compound **4i**

2-[(2-Chloro-phenyl)-(2-fluoro-phenylsulfanyl)-methyl]-3-hydroxy-5,5-dimethyl-cycl ohex-2-enone, white solid; m.p. 139-140°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.72 (s, 1H, -OH), 7.54-7.51 (m, 1H, Ar-H), 7.46-7.42 (m, 2H, Ar-H), 7.32-7.29 (m, 1H, Ar-H), 7.26-7.24 (m, 2H, Ar-H), 7.13-7.07 (m, 2H, Ar-H), 6.44 (s, 1H, -CH-), 2.49 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.33 (d, *J* = 17.5 Hz, 1H, $-CH_2$-CO-), 2.19 (d, J = 16.1 Hz, 1H, $-CH_2$-C=C-), 2.13(d, J = 16.1 Hz, 1H, $-CH_2$-C=C-), 1.03 (s, 3H, $-CH_3$), 0.81 (s, 3H, $-CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.54, 172.72, 162.34, 160.70, 135.30, 135.26, 134.61, 133.15, 130.44, 129.99, 129.94, 129.36, 129.00, 127.81, 127.67, 127.19, 124.87, 124.85, 116.02, 115.87, 110.97, 50.69, 44.22, 40.83, 31.69, 29.27, 27.37. HRMS(ESI$^+$) $[M+H]^+$: calcd. for $C_{21}H_{21}ClFO_2S$: 391.0889; Found: 391.0926. IR (KBr) (ν_{max}, cm^{-1}): 3054, 2957, 1652, 1635.

4.2.10 Compound **4j**

2-[(2-Chloro-phenyl)-o-tolylsulfanyl-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-en one, faint yellow solid; m.p. 135-136°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ9.96 (s, 1H, -OH), 7.46-7.42 (m, 2H, Ar-H), 7.34 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.26-7.24 (m, 2H, Ar-H), 7.21 (d, *J* = 7.1 Hz, 1H, Ar-H), 7.18-7.13 (m, 2H, Ar-H), 6.44 (s, 1H, -CH-), 2.50(d, *J* = 17.5Hz, 1H, $-CH_2$-CO-), 2.49 (s, 3H, $-CH_3$), 2.32 (d, *J* = 17.5Hz, 1H, $-CH_2$-CO-), 2.19(d, *J* = 16.1 Hz, 1H, $-CH_2$-C=C-), 2.11(d, *J* = 16.1 Hz, 1H, $-CH_2$-C=C-), 1.04 (s, 3H, $-CH_3$), 0.88 (s, 3H, $-CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$)

δ196.50, 173.89, 138.62, 135.54, 134.58, 130.65, 130.45, 130.36, 129.86, 129.26, 129.21, 127.52, 127.23, 126.66, 111.08, 50.36, 43.65, 42.85, 31.77, 28.29, 27.81, 20.38. HRMS(ESI$^+$) $[M+H]^+$: calcd. for $C_{22}H_{24}ClO_2S$: 387.1140; Found: 387.1179. IR(KBr) (ν_{max}, cm^{-1}): 3066, 2959, 1639, 1613.

4.2.11 Compound **4k**

2-[(2-Chloro-phenyl)-(3-isopropyl-phenylsulfanyl)-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-e-none, faint yellow solid; m.p. 149-150^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ10.23 (s, 1H, -OH), 7.45-7.43 (m, 3H, Ar-H), 7.35-7.34 (m, 1H, Ar-H), 7.25-7.22(m, 2H, Ar-H), 7.19 (d, *J* = 8.1 Hz, 2H, Ar-H), 6.29 (s, 1H, -CH-), 2.88 (se, *J* = 6.9 Hz, 1H, -CH-$(CH_3)_2$), 2.53 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.32 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.17 (d, *J* = 16.1 Hz, 1H, -CH_2-C=C-), 2.11 (d, *J* = 16.1 Hz, 1H, -CH_2-C=C-), 1.23 (d, *J* = 6.9 Hz, 6H, -$(CH_3)_2$), 1.03 (s, 3H, -CH_3), 0.78 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.60, 173.78, 149.42, 135.69, 135.64, 134.50, 131.61, 130.40, 129.55, 129.17, 128.83, 128.79, 127.44, 127.15, 110.99, 50.38, 45.97, 43.74, 33.84, 31.87, 28.55, 27.39, 23.83, 23.82. HRMS (ESI$^+$) $[M+H]^+$: calcd. for $C_{24}H_{28}ClO_2S$: 415.1452; found: 415.1490. IR(KBr) (ν_{max} ,cm^{-1}): 3160, 2958, 1652, 1606.

4.2.12 Compound **4l**

2-[(2-Chloro-phenyl)-(4-fluoro-phenylsulfanyl)-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-enon-e, white solid; m.p. 147-148^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.99 (s, 1H, -OH), 7.52-7.50 (m, 2H, Ar-H), 7.46-7.44 (m, 1H, Ar-H), 7.37-7.36 (m, 1H, Ar-H), 7.25-7.24 (m, 2H, Ar-H), 7.04 (t, *J* = 8.6 Hz, 2H, Ar-H), 6.27 (s, 1H, -CH-), 2.52 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.35 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.19(d, *J* = 16.2 Hz, 1H, -CH_2-C=C-), 2.11(d, *J* = 16.2 Hz, 1H, -CH_2-C=C-), 1.04 (s, 3H, -CH_3), 0.87 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.45, 173.62, 163.67, 162.02, 135.26, 134.54, 133.85, 133.80, 130.47, 129.34, 128.71, 127.93, 127.90, 127.22, 116.54, 116.39, 110.76, 50.30, 46.36, 43.69, 31.75, 28.22, 27.77. HRMS (ESI$^+$) $[M+H]^+$: calcd. for $C_{21}H_{21}ClFO_2S$: 391.0889; Found: 391.0884, IR(KBr) (ν_{max}, cm^{-1}): 3055, 2955, 1652, 1622.

4.2.13 Compound **4m**

2-[(2-Chloro-phenyl)-(4-methoxy-phenylsulfanyl)-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-e-none, faint yellow solid; m.p. 160-161°C, ^{1}H NMR (600 MHz,) δ10.31 (s, 1H, -OH), 7.48 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.45-7.44 (m, 1H, Ar-H), 7.34-7.33 (m, 1H, Ar-H), 7.24-7.22 (m, 2H, Ar-H), 6.87 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.17 (s, 1H, -CH-), 3.81 (s, 3H, -OCH_3), 2.52 (d, *J* = 17.5Hz, 1H, -CH_2-CO-), 2.38 (d, *J* = 17.5Hz, 1H, -CH_2-CO-), 2.16 (d, *J* = 16.1Hz, 1H, -CH_2-C=C-), 2.10 (d, *J* = 16.1Hz, 1H, , -CH_2-C=C-), 1.04 (s, 3H, -CH_3), 0.88 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.55, 173.65, 160.19, 135.70, 134.52, 134.10, 130.41, 129.14, 128.62, 127.14, 123.10, 114.89, 110.91, 55.37, 50.35, 47.14, 43.76, 31.76, 28.17, 27.90. HRMS(ESI$^+$) $[M+H]^+$: calcd. for $C_{22}H_{24}ClO_3S$: 403.1089; found: 403.1132 IR(KBr) (ν_{max}, cm^{-1}): 3067, 2959, 1627, 1683.

4.2.14 Compound **4n**

2-[(2-Chloro-phenyl)-m-tolylsulfanyl-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-enone, faint yellow solid; m.p.158-159°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ10.18 (s, 1H, -OH), 7.46-7.44 (m, 1H, Ar-H), 7.36-7.35 (m, 1H, Ar-H), 7.29 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.25-7.22 (m, 2H, Ar-H), 7.21(d, *J* = 7.6 Hz, 1H, Ar-H), 7.10 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.32 (s, 1H, -CH-), 2.52 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.34 (s, 3H, -CH_3), 2.33 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.19 (d, *J* = 16.1 Hz, 1H, -CH_2-C=C-), 2.13 (d, *J* = 16.1 Hz, 1H, -CH_2-C=C-), 1.04 (s, 3H, -CH_3), 0.87 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, CDCl3) δ196.55, 173.83, 139.13, 135.59, 134.50, 132.51, 131.49, 130.42, 129.22, 129.09, 128.99, 128.78, 127.97, 127.18, 110.91, 50.37, 45.35, 43.75, 31.80, 28.40, 27.57, 21.31. HRMS(ESI$^+$) $[M+H]^+$: calcd. for $C_{22}H_{24}ClO_2S$: 387.1140; Found: 387.1177, IR(KBr) (vmax, cm-1): 3122, 2959, 1627, 1683.

4.2.15 Compound **4o**

3-Hydroxy-2-[(4-methoxy-phenyl)-m-tolylsulfanyl-methyl]-5,5-dimethyl-cyclohex-2-enone, faint yellow solid; m.p. 102-103°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.57 (s, 1H, -OH), 7.37 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.23(s, 1H, Ar-H), 7.21-7.19 (m, 1H, Ar-H), 7.06 (d, *J* = 7.1 Hz, 1H, Ar-H), 7.02 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.88(d, *J* = 8.6 Hz, 2H, Ar-H), 6.12 (s, 1H, -CH-), 3.81 (s, 3H -OCH_3), 2.46 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.33(d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.32 (s, 3H, -CH_3), 2.19 (d, *J* = 16.1Hz, 1H,

-CH_2-C=C-), 2.09 (d, *J* = 16.1Hz, 1H, -CH_2-C=C-), 1.03 (s, 3H, -CH_3), 0.78 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.69, 173.12, 159.18, 138.94, 136.77, 132.84, 131.31, 129.66, 129.19, 128.93, 128.60, 127.76, 126.47, 114.23, 50.37, 45.90, 43.49, 31.76, 28.55, 27.34, 21.25. HRMS (ESI^+) $[M+H]^+$: calcd. for $C_{23}H_{27}O_3S$: 383.1636; Found: 383.1617. IR (KBr) (ν_{max}, cm^{-1}): 3057, 2961, 1652, 1623.

4.2.16 Compound **4p**

2-[(4-Chloro-phenyl)-(4-methoxy-phenylsulfanyl)-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-enone, white solid; m.p. 164-165°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.60 (s, 1H, -OH), 7.39 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.37 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.30 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.85 (d, *J* = 7.9 Hz, 2H, Ar-H), 5.97 (s, 1H, -CH-), 3.80 (s, 3H, -OCH_3), 2.46 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.28 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.17 (d, *J* = 16.0 Hz, 1H, -CH_2-C=C-), 2.06 (d, *J* = 16.0 Hz, 1H, -CH_2-C=C-), 1.02 (s, 3H, -CH_3), 0.80 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.63, 173.22, 160.10, 136.56, 133.99, 133.55, 129.33, 128.93, 122.80, 114.83, 111.32, 55.38, 50.28, 47.36, 43.49, 31.73, 28.26, 27.72. HRMS(ESI^+) $[M+H]^+$: calcd. for $C_{22}H_{24}ClO_3S$: 403.1089; Found: 403.1128. IR (KBr) (ν_{max} ,cm^{-1}): 3064, 2961, 1652, 1635.

4.2.17 Compound **4q**

2-[(4-Chloro-phenyl)-(4-fluoro-phenylsulfanyl)-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-enone, faint yellow solid; m.p. 154-155°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ10.00 (s, 1H, -OH), 7.52-7.50 (m, 2H, Ar-H), 7.46-7.44 (m, 1H, Ar-H), 7.36-7.35 (m, 1H, Ar-H), 7.26-7.24 (m, 2H, Ar-H), 7.04 (t, *J* = 8.6 Hz, 2H, Ar-H), 6.27 (s, 1H, -CH-), 2.52 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.35 (d, *J* = 17.5 Hz, 1H, -CH_2-CO-), 2.18 (d, *J* = 16.1 Hz, 1H, -CH_2-C=C-), 2.12 (d, *J* = 16.1 Hz, 1H, -CH_2-C=C-), 1.04 (s, 3H, -CH_3), 0.87 (s, 3H, -CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.47, 173.64, 163.69, 162.03, 135.20, 133.86, 133.81, 130.50, 129.37, 127.86, 127.84, 127.24, 116.55, 116.41, 110.71, 50.29, 46.37, 43.69, 31.75, 28.22, 27.76. HRMS(ESI^+) $[M+H]^+$: calcd. for $C_{21}H_{21}ClFO_2S$: 391.0889; Found: 391.0867 IR(KBr) (ν_{max}, cm^{-1}): 3069, 2961, 1683, 1662.

4.2.18 Compound **4r**

2-[(4-bromo-phenyl)-(4-fluoro-phenylsulfanyl)-methyl]-3-hydroxy-5,5-dimethyl-cyclohex-2-enone, faint yellow solid; m.p.175-176 °C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.32 (s, 1H, -OH), 7.48-7.47 (m, 2H, Ar-H), 7.43-7.41 (m, 2H, Ar-H), 7.31-7.30 (m, 2H, Ar-H), 7.03-7.01 (m, 2H, Ar-H), 6.04 (s, 1H, -CH-), 2.46 (d, J = 17.5 Hz, 1H, $-CH_2$-CO-), 2.25 (d, J = 17.5 Hz, 1H, $-CH_2$-CO-), 2.19 (d, J = 16.1 Hz, 1H, $-CH_2$-C=C-), 2.07 (d, J = 16.1 Hz, 1H, $-CH_2$-C=C-), 1.02 (s, 3H, $-CH_3$), 0.79 (s, 3H, $-CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.75, 175.01, 163.46, 161.82, 137.48, 133.77, 133.71, 132.01, 129.63, 127.61, 127.58, 121.91, 116.30, 116.15, 112.66, 47.00, 36.47, 29.75, 20.25. HRMS(ESI$^+$) $[M+H]^+$: calcd. for $C_{21}H_{21}BrFO_2S$: 435.0384; Found: 435.0420. IR(KBr) (ν_{max}, cm^{-1}): 3064, 2956, 1652, 1634.

4.2.19 Compound **4x**

2-[(4-Fluoro-phenylsulfanyl)-phenyl-methyl]-3-hydroxy-cyclohex-2-enone, white solid; m.p.150-151 °C, ^{1}H NMR (600 MHz, $CDCl_3$) δ9.29 (s, 1H, -OH), 7.45-7.44 (m, 2H, Ar-H), 7.42-7.40 (m, 2H, Ar-H), 7.36-7.34 (m, 2H, Ar-H), 7.30-7.29 (m, 1H, Ar-H), 7.03-7.00 (m, 2H, Ar-H), 6.13(s, 1H, -CH-), 2.56 (dt, J_1 = 17.8 Hz, J_2 = 5.5 Hz, 1H, $-CH_2$-CO-), 2.41 (dt, J_1 = 17.8 Hz, J_2 = 5.5 Hz, 1H, $-CH_2$-CO-), 2.32-2.37 (m, 1H, $-CH_2$-C=C-), 2.18-2.12 (m, 1H, $-CH_2$-C=C-), 1.95-1.88 (m, 1H,-C-CH_2-C), 1.86-1.80 (m, 1H, -C-CH_2-C). ^{13}C NMR (150 MHz, $CDCl_3$) δ196.75, 175.01, 163.47, 161.82, 137.48, 133.77, 133.71, 128.87, 128.06, 128.04, 127.89, 126.48, 116.30, 116.15, 112.66, 47.00, 36.47, 29.75, 20.25. HRMS (ESI$^+$) $[M+H]^+$: calcd. for $C_{19}H_{18}FO_2S$: 329.1011, Found: 329.1020. IR (KBr) (ν_{max}, cm^{-1}): 3075, 2948, 1670, 1635.

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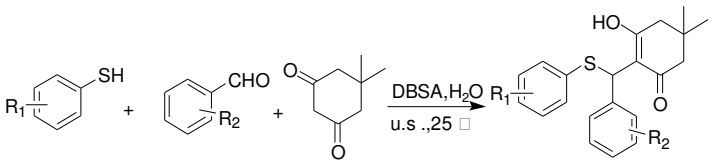
Captions of schemes and tables

Scheme 1. One-pot three-component synthesis of the title compound

Scheme 2 The proposed mechanism of one-pot three-component reaction of aldehyde, thiophenol and 5,5-dimethyl-1,3-cyclohexane-dione

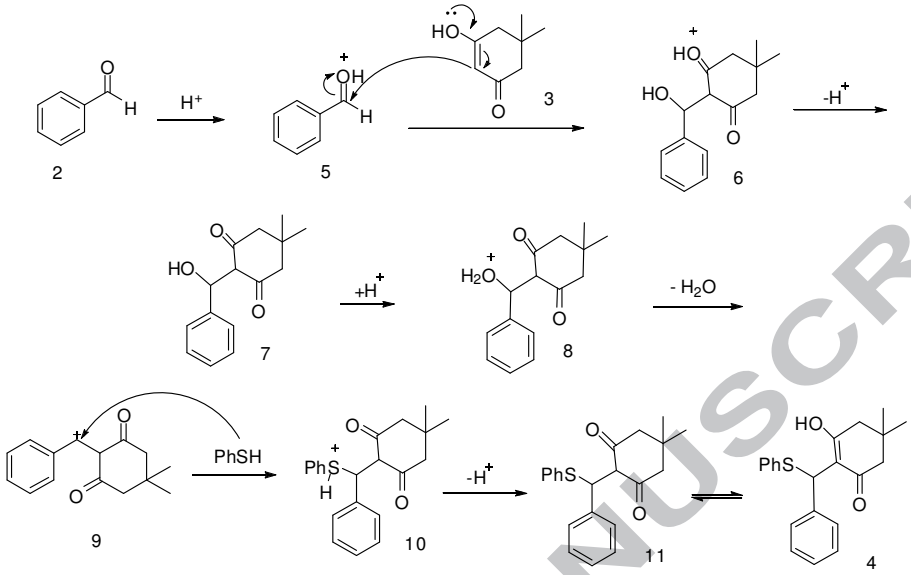
Table 1 Effect of reaction conditions on the synthesis of **4a** under ultrasound irradiation

Table 2 Synthesis of 3-hydroxy-5,5-dimethyl-2-[phenyl(phenylthio)methyl] cyclohex-2-enone catalyzed by DBSA under ultrasound and without ultrasound



1 2 3 4

Scheme 1. One-pot three-component synthesis of the title compound



Scheme 2 The proposed mechanism of one-pot three-component reaction of aldehyde, thiophenol and 5,5-dimethyl-1,3-cyclohexane-dione

Table 1 Effect of reaction conditions on the synthesis of **4a** under ultrasound irradiation [a]

Entry	Amount of DBSA (mol %)	Frequency (Hz)	Temp. (^{o}C)	Molar ratio of 1:2:3	Time (min)	Isolated Yield (%)
1	15	40	25	1:1:1	100	79
2	10	40	25	1:1:1	100	79
3	7.5	40	25	1:1:1	100	68
4	5	40	25	1:1:1	120	60
5	0	40	25	1:1:1	150	45
6	10	40	25	1:1:1.2	100	80
7	10	40	25	1:1.2:1.2	120	82
8	10	25	25	1:1:1	140	60
9	10	40	40	1:1:1	80	55
10	10	40	50	1:1:1	80	50
11	10	-	25	1:1:1	180	63[b]

[a]Substrate: 4-fluorothiophenol(1mmol); H_2O (2 mL)

[b]Stirring alone without ultrasound.

Table 2 Synthesis of 3-hydroxy-5,5-dimethyl-2-[phenyl(phenylthio)methyl] cyclohex-2-enone catalyzed by DBSA under ultrasound and without ultrasound [a]

Entry	R_1	R_2	Ultrasound irradation		Conventional stirring	
			Time/min	Isolated yield/%	Time/min	Isolated yield/%
4a	4-F	H	90	79	180	63
4b	4-OCH_3	H	60	89	150	77
4c	2-F	H	110	80	210	61
4d	2-CH_3	H	70	85	180	64
4e	4-CH_3	H	70	88	150	65
4f	2, 4-dimethyl	H	80	80	190	54
4g	2, 4-dichlorine	H	100	76	210	51
4h	2, 4- dimethyl	2-Cl	90	82	150	53
4i	2-F	2-Cl	60	86	120	77
4j	2-CH3	2-Cl	100	72	180	52
4k	3-$CH(CH_3)_2$	2-Cl	120	82	240	77
4l	4-F	2-Cl	90	86	180	76
4m	4-OCH_3	2-Cl	70	82	120	56
4n	3-CH_3	2-Cl	120	72	200	48
4o	3-CH_3	4-OCH_3	110	70	200	56
4p	4-OCH_3	4-Cl	120	75	180	40
4q	4-F	4-Cl	70	90	180	71
4r	4-F	4-Br	30	92	90	86
4s	2-NH_2	H	120	---	480	---
4t	4-OH	H	120	---	480	---
4u	4-F	4-OH	120	---	480	---
4v	2, 5- dimethyl	H	120	---	480	---
4w	4-F	4-NO_2	120	---	480	---
4x	4-F	H	180	20	720	5

[a] 4a-4w: thiophenol, 1mmol; arylaldehyde, 1mmol; 5,5-dimethyl-1,3-cyclohexanedion-dione; 4x thiophenol, 1mmol; arylaldehyde, 1mmol; 1,3-cyclohexanedion-dione, 1mmol; DBSA, 0.1 mmol; H_2O, 2 mL