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Preparation of some alkenoic acid derivatives as new plant growth regulators

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Abstract A number of 3-alkoxy-5-substituted-2,4-alkadienoic acids (**4a–f**) have been synthesized from the reaction of ethyl (*E*)-3-alkoxy-2-butenoate with different ketones in the presence of KOH in DMSO. Similarly, several (2*Z*,4*E*)-5-[4-(benzylthio)phenyl]-3-alkoxyhexa-2,4-dienoic acids were prepared via condensation of ethyl (*E*)-3-alkoxy-2-butenoate with 4-(benzylthio)acetophenone in the presence of KOH in DMSO. The structures of all synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and MS spectra and by elemental analysis.

Keywords 2,4-Alkadienoic acids · Ethyl (*E*)-3-alkoxy-2-butenoate · KOH/DMSO · Plant growth regulators

Introduction

Pentadienoic acids (PDAs) and hexanedienoic acids (HDAs) have attracted considerable interest in recent years due to their relationship with the important plant hormone abscisic acid (ABA) (**1**) and the presence of a diene system in their molecules. In this respect, it is worth mentioning that abscisic acid, which is the most common 2,4-pentadienoic acid, isolated from the young cotton fruit [1], has been employed as plant antitranspirant [2]. Some other related compounds have been used as antioxidants [3] and as effective plant hormones to inhibit rice germination [4, 5]. Other PDA derivatives exhibit a wide spectrum of pharmacological effects and have several useful industrial applications. Some PDA compounds are used in medicinal

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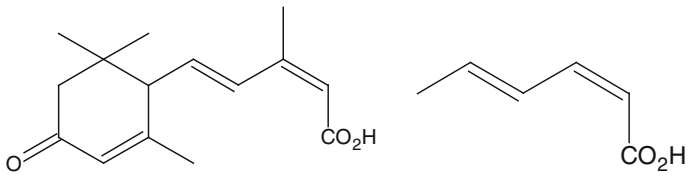
chemistry as antidiabetic agents with a high serum glucose-reducing activity [6, 7], while others are employed as hyperuricemia agents to reduce plasma uric acid levels [8], useful in the treatment of liver disorder [9], and have retinoid-like biological activity [10, 11]. Moreover, other derivatives are useful in industry as adhesive compounds [12, 13], and sunscreens [14]. In addition, some PDAs are used as plant growth regulators [15].

Alternatively, some derivatives are used as ultraviolet light absorbents in cosmetic manufacturing and in skin disease therapy [16, 17], while others are important in chemotherapy for the treatment of inflammations, atherosclerosis, restenosis, and immune disorders such as arthritis, transplant rejection [18], and antimalarial agents [19]. Also, other PDAs are used as starting materials for the manufacturing of penicillin [20]. Furthermore, some of these acids show antitranspirant activity either as free acids [21] or when applied as sodium or ammonium salts [22]. Nanzyo and co-workers reported that some PDA derivatives have a growth inhibitory activity on rice seedings [23], whereas amide derivatives of pentadienoic acid have been used as antagonists of platelet activating factor [24], antiallergic agents [25], as bactericides and fungicides [26, 27], to inhibit microbial growth storage in mango pulp [28], and to prevent the excessive bone resorption associated with osteoporosis [29–31], or as blood platelet aggregation inhibitors [32].

HDAs, on the other hand, exhibit a wide range of biological activities. It has been reported that some HDA derivatives have been used as antimicrobial agents [33], insecticidal [34], while others were used in chemotherapy and showed good antiproliferative properties [35]. Sorbic acid (2) (Fig. 1) is one of the most common 2,4-hexadienoic acids with interesting biological activities, was first isolated from unripe berries of Rowan (*Sorbus aucuparia*), and has been used as a food preservative [36]. Some sorbic acid derivatives showed a wide range of antimicrobial activities against spoilage bacteria [36], while others are used in the food industry as preservatives [37], and as effective antifungal agents [38].

The biological importance of alkenoic acids has stimulated an intensive research work for the synthesis of many new derivatives [4]. In addition to being present in various naturally occurring compounds with a wide range of biological and pharmaceutical activities, these acids have also been shown, in many cases, to serve as effective synthons in the construction of a wide variety of interesting molecules [39]. The high cost resulting from a long and difficult synthesis of alkenoic acids as plant growth regulators [40] prompted researchers to develop new methods for the



(A) **(B)**

Fig. 1 Abscisic acid (**A**) and Sorbic acid (**B**) structures

synthesis of these important molecules. The reaction of phosphorous, arsenic, or tellurium ylides with some aldehydes and ketones afforded the corresponding alkenoic acids through Wittig-type reactions [41–43]. In addition, synthesis of some alkenoic acids has been achieved through Stille coupling, Reformatsky, and Vilsmeier Haak reactions [44, 45]. Similarly, condensation of ethyl (2*E*)-3-alkoxybut-2-enoate (**3a** and **3b**) with carbonyl compounds, mainly aldehydes, in tellurium ylidespresence of several bases, such as sodium hydride [46], lithium diisopropylamide (LDA) [47], and lithium or sodium amide [48, 49], has been used to prepare some of these acids. In view of the wide interest in the chemistry of alkenoic acids, and within the framework of research related to the chemistry of synthesis of ethyl (2*E*)-3-alkoxybut-2-enoate (**1a** and **1b**), the synthesis and characterization of a number of new alkenoic acid derivatives with expected biological activities are discussed.

Experimental

Materials and equipments

All chemicals used were obtained from commercial sources and were used as received without further purification. Progress of reactions was monitored by thin layer chromatography (TLC) using glass plates pre-coated with silica gel (Merck Kiesegel 60 F254 layer thickness 0.25 mm). Melting points were measured on a Stuart scientific melting point apparatus in open capillary tubes. Infrared spectra (IR) were obtained, as potassium bromide (KBr) discs, on Nicolet-MAGNA-IR-560 spectrophotometer; only characteristic peaks are indicated in wave number (cm^{-1}).

^{1}H and ^{13}C NMR spectra were acquired with the aid of a Bruker DPX 300 MHz spectrometer (Germany) with DMSO-d_6 as solvent and TMS as the internal standard. Peak multiplicities of the signals are abbreviated as follows: s-singlet, d-doublet, t-triplet, q-quartet, and m-multiplet. Chemical shifts are expressed in δ units; *J* values for ^{1}H–^{1}H coupling constants are given in Hertz. High resolution mass spectra (HRMS) were obtained using an electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-4 (7-Tesla) instrument (Bremen, Germany). The samples were dissolved in acetonitrile, diluted in spray solution (methanol/water 1:1 v/v +0.1 % formic acid), and infused using a syringe pump with a flow rate of 2 mL min^{-1}. External calibration was conducted using an arginine cluster in a mass range *m/z* 175–871. Elemental analyses were performed on a Euro-Vector Euro, C, H, N, and S elemental analyzer (EA3000); the obtained results agreed with the calculated percentages to within ±0.4 %. Compounds were checked for their purity by TLC using glass plates, precoated with silica gel 60 GF254, supplied by Fluka.

General procedure for preparation of ethyl (2E)-3-alkoxybut-2-enoate (**3a** and **3b**)

Compounds **3a** and **3b** were synthesized and purified according to the general procedure described by Mubarak and co-workers which involves reacting ethyl

acetoacetate (**1**) (19.5 g, 0.15 mol) with each of trimethyl orthoformates (**2a**) and with triethyl orthoformates (**2b**) (0.15 mol) in methanol (15 mL). Concentrated hydrochloric acid HCl (0.07 mL) was added, and the mixture was immediately distilled to give ethyl (2*E*)-3- methoxyoxybut-2-enoates (**3a**) and ethyl (2*E*)-3-ethoxyoxybut-2-enoates (**3b**) [50].

*Ethyl (2E)-3-methoxybut-2-enoate (**3a**)*

Yield: 21.0 g, 96 %; b.p. = 182–192 °C, (lit. 188–196 °C) [39].

*Ethyl (2E)-3-ethoxybut-2-enoate (**3b**)*

Yield: 21.3 g, 91 %; b.p. = 186–195 °C, (lit. 193–196 °C) [39].

General procedure for preparation of 3-alkoxy-5-substituted-2,4-alkadienoic acids (**4a–f**)

Compounds **4a–f** were synthesized and purified according to the following general procedure. To a solution of (10.0 mol) of each of ethyl (2*E*)-3-methoxybut-2-enoates (**3a**) and ethyl (2*E*)-3-ethoxybut-2-enoates (**3b**) in 5.0 mL of dimethyl sulphoxide (DMSO) were added 10.0 mmol of the corresponding ketone and 0.56 g (10.0 mmol) of potassium hydroxide. The mixture was heated for 4–6 h at 100 °C; completion of the reaction was checked by TLC with dichloromethane, DCM or (hexane/ethyl acetate) as eluents. After cooling, the mixture was diluted with water and the by-products were extracted with diethyl ether. The aqueous layer was acidified with dilute hydrochloric acid and the precipitated product was filtered, washed with water, and dried to give the desired products. The following compounds were synthesized according to the afroementioned general procedure.

*(2Z)-3-Methoxy-5,5-diphenylpenta-2,4-dienoic acid (**4a**)*

Yield: 1.12 g, 40 %; m.p. 157–159 °C. IR (KBr): 3,444, 2,936, 1,680, 1,608, 1,550, 1,183 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.23 (s, 3H), 5.13 (s, 1H), 7.34 (m, 11 H), 11.72 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 55.5, 94.9, 121.6, 127.8, 128.1, 128.3, 128.8, 129.3, 129.6, 140.6, 142.4, 147.5, 167.7, 168.3 ppm. HRMS *m/z*: $[M + Na]^+$ calcd. for $C_{18}H_{16}NaO_3$ 303.09994; found: 303.09917. Anal. calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.44; H, 5.82.

*(2Z,4E)-3-Methoxy-5-phenylhexa-2,4-dienoic acid (**4b**)*

Yield: 0.92 g, 42 %; m.p. 166–168 °C. IR (KBr): 3,446, 2,929, 1,685, 1,624, 1,567, 1,202 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H), 3.71 (s, 3H), 5.16 (s, 1H), 7.82 (m, 6H), 11.5 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 18.7, 55.8, 94.0, 115.5, 120.7, 128.4, 128.5, 139.9, 142.4, 168.2, 168.3 ppm. HRMS *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{14}NaO_3$ 241.08406; found: 241.08367. Anal. calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.88; H, 6.62.

*(2Z,4E)-3-Methoxy-5-(4-methylphenyl) hexa-2,4-dienoic acid (**4c**)*

Yield: 0.93 g, 41 %; m.p. 158–160 °C. IR (KBr): 3,444, 2,917, 1,671, 1,623, 1,564, 1,175 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.24 (s, 3H), 2.50 (s, 3H), 3.71 (s, 3H), 5.13 (s, 1 H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.26 (s, 1H), 11.3 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 18.6, 21.1, 55.8, 93.7, 119.9, 126.3, 129.4, 137.9, 140.6, 143.5, 168.2, 168.6 ppm. HRMS *m/z*: $[M + Na]^+$ calcd. for $C_{14}H_{16}NaO_3$ 255.09995; found 255.09917. Anal. calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.31; H, 7.20.

*(2Z)-3-Ethoxy-5,5-diphenylpenta-2,4-dienoic acid (**4d**)*

Yield: 0.97 g, 33 %; m.p. 159–161 °C. IR (KBr): 3,425, 2,929, 1,668, 1,614, 1,557, 1,181 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.56 (t, $J = 6.8$ Hz, 3H), 3.52 (q, $J = 6.6$, 13.4 Hz, 2H), 5.12 (s, 1H), 7.24 (m, 11 H), 11.68 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 13.5, 3.7, 95.0, 121.6, 127.6, 128.1, 128.2, 128.9, 129.2, 129.5, 141.1, 142.3, 147.7, 166.9, 168.4 ppm. HRMS *m/z*: $[M + Na]^+$ calcd. for $C_{19}H_{18}NaO_3$ 317.11559; found: 317.11482. Anal. calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.11; H, 6.17.

*(2Z,4E)-3-Ethoxy-5-phenylhexa-2,4-dienoic acid (**4e**)*

Yield: 1.18 g, 51 %; [m.p 144–146 °C. IR (KBr): 3,445, 2,990, 1,668, 1,618, 1,558, 1,191 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.36 (t, $J = 6.8$ Hz, 3H), 2.29 (s, 3H), 3.94 (q, $J = 6.7$, 13.7 Hz, 2H), 5.17 (s, 1H), 7.68 (m, 6 H). 11.60 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 14.5, 18.6, 64.2, 94.2, 120.8, 126.5, 128.4, 128.8, 143.6, 143.7, 167.6, 168.5 ppm. HRMS *m/z*: $[M + Na]^+$ calcd. for $C_{14}H_{16}NaO_3$ 255.09995; found: 255.09917. Anal. calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.42; H, 7.00.

*(2Z,4E)-3-Ethoxy-5-(4-methylphenyl) hexa-2,4-dienoic acid (**4f**)*

Yield:1.0 g, 41 %; [m.p. 160–162 °C. IR (KBr): 3,446, 2,923, 1,681, 1,620, 1,559, 1,198 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.43 (t, $J = 6.3$ Hz, 3H), 2.27 (s, 3H), 2.30 (s, 3H), 3.91 (q, $J = 6.7$, 13.5 Hz 2H), 5.11 (s, 1H), 7.18 (d, $J = 7.3$ Hz, 2H), 7.38 (d, $J = 7.2$ Hz, 2H), 7.31 (s, 1H), 11.55 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 14.5, 18.6, 21.0, 64.1, 93.9, 120.0, 126.3, 129.4, 137.8, 140.8, 143.6, 167.8, 168.3 ppm. HRMS *m/z*: $[M + Na]^+$ calcd. for $C_{15}H_{18}NaO_3$ 269.11560; found: 269.11482. Anal. calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.31; H, 7.32.

Synthesis of 4-(benzylthio)acetophenone (**7**)

Potassium hydroxide (1.50 g, 26.6 mol) was added to a solution of benzyl thiol (**6**) (3.13 mL, 26.6 mmol) in 15.0 mL of ethanol. The mixture was heated to reflux until

the KOH had completely dissolved and was then cooled to room temperature. A solution of 4-fluoroacetophenone (**5**) (3.25 mL, 26.6 mol) in 15.0 mL of ethanol was then added drop-wise and the mixture was heated to reflux for 7 h; completion of reaction was checked by TLC (in DCM). When cooled to room temperature, the precipitate was filtered and washed with water and recrystallized from ethyl acetate to afford the desired product, **7**, as white needles. Yield: 5.8 g, 90 % Yield; m.p. 112–114 °C (lit. 110–112 °C) [52].

General procedure for preparation of (2Z,4E)-5-[4-(benzylthio)-phenyl]-3-alkoxyhexa-2,4-dienoic acids (**8a**, **b**)

To a solution of (5.0 mmol) of each of **3a** and **3b** in 3.0 mL of dimethyl sulphoxide (DMSO) were added (5.0 mmol) of 4-(benzylthio)acetophenone (**7**) and (0.28 g, 5.0 mol) of potassium hydroxide and the mixture was heated for about 6 h at 100 °C; completion of the reaction was checked by TLC. After cooling, the mixture was diluted with water and the by-products were removed by extraction with diethyl ether. The aqueous layer was acidified with dilute HCl and the precipitated product was filtered, washed with water, and dried to give the desired products. The following compounds were synthesized according to the above mentioned general procedure.

*(2Z,4E)-5-[4-(Benzylthio)phenyl]-3-methoxyhexa-2,4-dienoic acid (**8a**)*

Yield: 1.16 g, 68 %; [m.p. 140–142 °C. IR (KBr): 3,446, 2,924, 1,678, 135, 153, 1,176 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.22 (s, 3H), 3.71 (s, 3H), 4.27 (s, 2H), 5.14 (s, 1H), 7.39 (m, 10H), 11.3 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 18.4, 36.8, 55.8, 94.0, 120.3, 126.9, 127.5, 128.3, 128.8, 129.2, 136.8, 137.8, 140.7, 142.8, 168.2, 168.4 ppm. HRMS *m/z*: $[M + Na]^+$ calcd. for $C_{20}H_{20}NaO_3S$ 363.10308; found 363.10254. Anal. calcd. for $C_{20}H_{20}O_3S$: C, 70.56; H, 5.92; S, 9.42. Found: C, 70.56; H, 6.06; S, 9.42. 9.72.

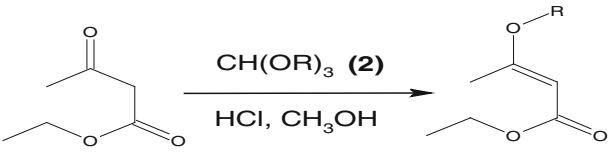
*(2Z,4E)-5-[4-(benzylthio)phenyl]-3-ethoxyhexa-2,4-dienoic-acid (**8b**)*

Yield 1.15 g, 65 %; m.p. 139–141 °C. IR (KBr): 3,447, 2,985, 1,680, 137, 1,562, 1,198 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.33 (t, $J = 5.7$ Hz, 3H), 2.26 (s, 3H), 3.96 (q, $J = 6.7$, 13.3 Hz, 2H), 4.27 (s, 2H), 5.15 (s, 1H), 7.33 (m, 10H), 11.58 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 14.5, 18.4, 36.8, 64.2, 94.2, 120.3, 126.9, 127.5, 128.3, 128.8, 129.2, 136.8, 137.8, 140.9, 142.8, 168.3, 168.4 ppm. HRMS *m/z*: $[M + Na]^+$ calcd. for $C_{21}H_{22}NaO_3S$ 377.11896, found: 377.11819. Anal. calcd. for $C_{21}H_{22}O_3S$: C, 71.16; H, 6.26; S, 9.05. Found: C, 71.30; H, 5.97; S, 8.97.

Results and discussion

Chemistry

Ethyl (2*E*)-3-alkoxybut-2-enoate (**3a** and **3b**), required in this study were efficiently synthesized according to a procedure described by Mubarak and coworkers [50] (equation **1**) which involves the reaction of ethyl acetoacetate (**1**) and trialkyl orthoformate (**2a** and **2b**), followed by the addition of concentrated hydrochloric acid. Immediate distillation of the reaction mixture afforded the desired product as a mixture of *E*- and *Z*- isomers with the *E*- isomer as the major product, in excellent yields: 96 % for **3a** and 91 % for **3b**. Syntheses of 3-alkoxy-5-substituted-2,4-alkadienoic acids (**4a**–**f**) were carried out via the route shown in Scheme 1. Thus, treatment of **3a** or **3b** with ketones in DMSO and in the presence of KOH yielded alkadienoic acids with good yields as depicted in Scheme 1, presumably through 2-oxo-5,6-dihydro-2H-pyrans as intermediate in the reaction; these intermediates were not isolated but they have been previously reported [39, 51].

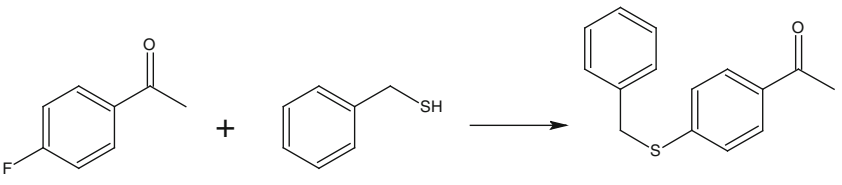


(1)

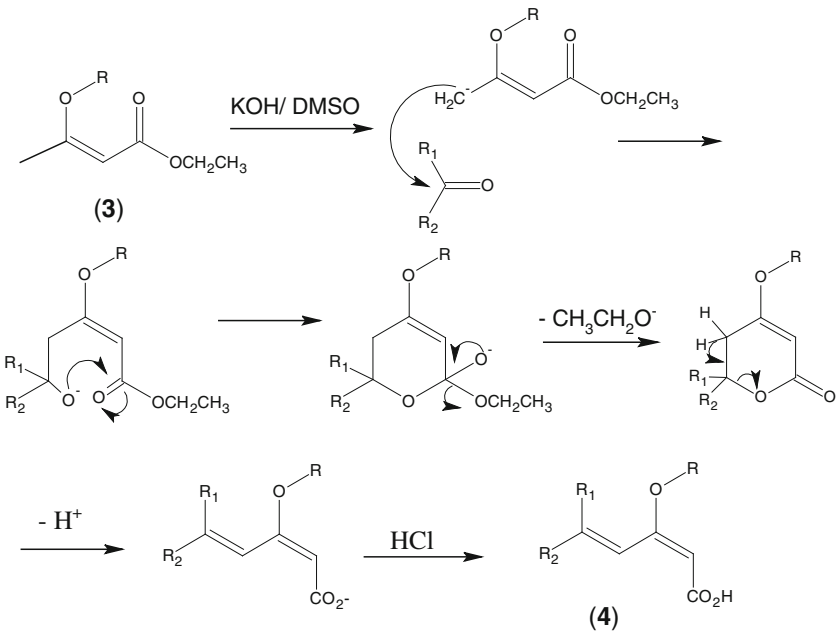
Compounds **2** and **3**

	a	b
R	CH_3	CH_3CH_2

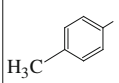
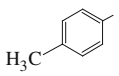
Similarly, 4-(benzylthio)acetophenone (**7**) was synthesized in 90 % yield through nucleophilic aromatic substitution reaction S_NAr, (addition–elimination mechanism) according to a procedure outlined by Mulder et al. [52] as shown from the reaction of 4′-fluoroacetophenone (**5**) and benzyl thiol (**6**) in the presence of KOH. Treatment of **7** with each of **3a** and **3b** in DMSO and in presence of KOH gave the desired products; (2*Z*,4*E*)-5-[4-(benzylthio)phenyl]-3-alkoxyhexa-2,4-dienoic acids (**8a** and **8b**) in moderate yields (65–68 %).



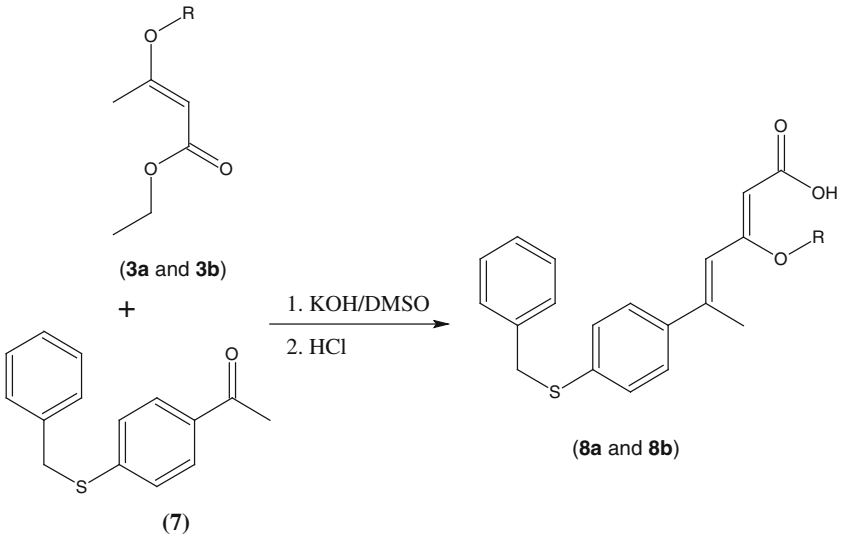
(2)



Compounds (**4a-f**)

	a	b	c	d	e	f
R_1		CH_3-	CH_3-		CH_3-	CH_3-
R_2						
R	CH_3			CH_3CH_2		

Scheme 1 Preparation of compounds **4a–f**



(3)

The structures of the prepared compounds were confirmed by NMR, mass spectrometry, IR, and elemental analysis. These data, detailed in "Experimental", are consistent with the suggested structures. The ^{1}H and ^{13}C NMR spectra of all prepared compounds are in total agreement with their assigned structures. DEPT experiments were employed to differentiate secondary and quaternary carbons from primary and tertiary ones. Additional supports of the proposed structures come from mass spectral data. From the mass spectra display, the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with the calculated values as suggested by their molecular formulas. In addition, IR spectra of the synthesized compounds showed absorption bands corresponding to the different functional groups present.

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