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One-Pot Preparation of 3,5-Hexadienoic Acid Compounds from Phenylacetaldehyde Derivatives

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ONE-POT PREPARATION OF 3,5-HEXADIENOIC ACID COMPOUNDS FROM PHENYLACETALDEHYDE DERIVATIVES

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Abstract : The synthesis of 6-aryl-4-methoxycarbonyl-3-methyl-3,5-hexadienoic acids by condensation of dimethyl-3-methyl glutaconate and phenylacetaldehyde derivatives in a stereoselective process is described.

Methyl 6-aryl 3-methyl 3,5 hexadienoates are important intermediates for the synthesis of natural products [1,2]. Preparative procedures for these compounds reported in the literature are laborious[3]. We report herein a convenient method for synthesis of 6-aryl-4- methoxycarbonyl-3-methyl-3,5-hexadienoic acid derivatives which consists in a one pot reaction of phenylacetaldehyde derivatives with dimethyl-3-methylglutaconate. It is

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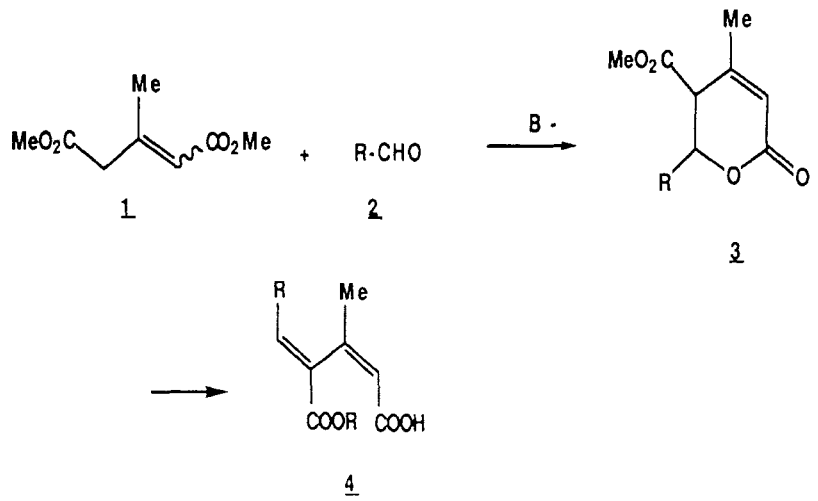
Scheme 1



R = alkyl, aryl, styryl, cinnamyl.

R' = H or Me

known that dimethyl-3-methylglutaconate 1 reacts with aldehydes under basic conditions to yield 2,4-dienoic acids[4-8] 4 , presumably by way of the corresponding lactones[9] 3 (scheme 1).

We used this procedure to condense phenylacetaldehyde derivatives 5 with compound 1 . These compounds possess an acidic proton and isomerism of 2,4-dienoic acids 6 to 3,5-dienoc acids 7 is possible. A variety of aldehydes were used, 5a, 5e-f were commercially available . The aldehydes 5b-d were prepared by reduction of the corresponding acyl chloride with sodium tetrahydroborate and $CdCl_2$-1.5 DMF according to the method previously described[10] . The results of condensation are reported in the table.

Table

7	R	Ar	Yield * (%)
a	H	Ph	85
b	H	p.MePh	60
c	H	p.MeOPh	65
d	H	p.F-Ph	60
e	Me	Ph	65
f	Ph	Ph	65

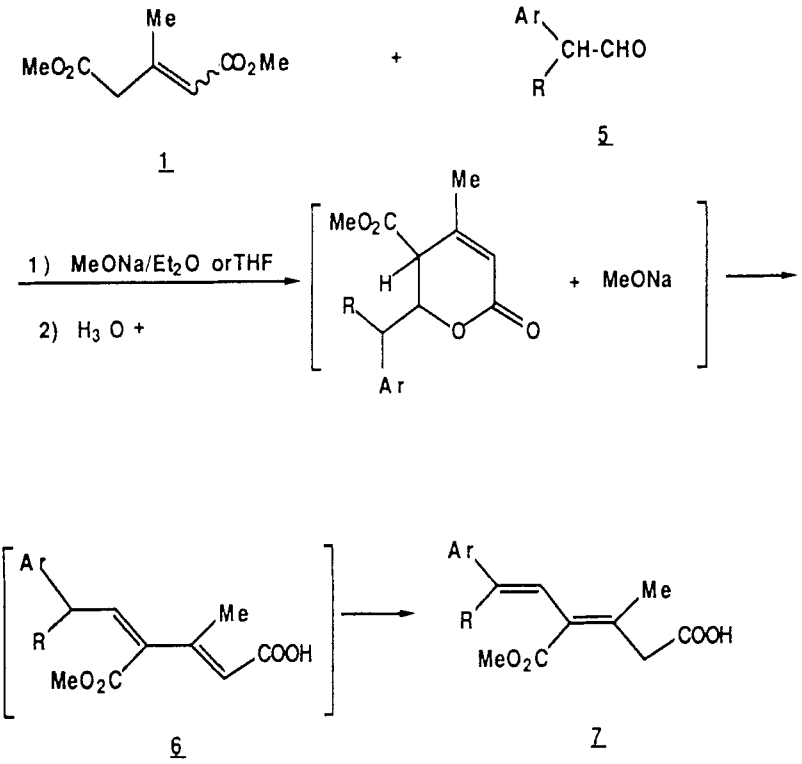
* Isolated yields after recrystallization.

The condensation of aldehydes with methyl-3-glutaconate was performed with sodium methylate in ether or tetrahydrofuran according to our methodology for the same reaction with ketones[11] (scheme 2)

The formation of acidic compounds suggests that the reaction proceeds via initial formation of the lactone, followed by cleavage of pyrone ring by generated sodium methylate according to the mechanism for condensation of aldehydes[9] and ketones[12].

The structure of compounds 6 was identified by mechanistic considerations and NMR. Spectroscopic data, cited in the experimental, indicated that the 5 C=C of compounds 7a-d possesses an E configuration (J = 16 Hz).

Scheme 2



NOE experiments showed that irradiation of methyl protons in position 3 caused an increase in the intensity of the signal for the proton in position 5 suggesting a 3 Z configuration.

These dienoic acids 7 (3Z, 5E) are probably owing to an evolution, in basic media, to a more stable form, than 2,4-dienoic acids.

Experimental

Phenylacetaldehydes 5

The following procedure is typical of the experimental conditions used for the preparation of phenylacetaldehydes derivatives.

4-methoxyphenylacetaldehyde 5c

A solution of 5 g (30 mmol) of 4-methoxyphenylacetic acid and 5.25 mL (60 mmol) of oxalyl chloride in benzene (15 mL) was stirred at room temperature for 3 h. Evaporation of benzene under reduced pression gave the acyl chlorid (yield 98 %).

10 g (54.5 mmol) of cadmium chloride were added to 35 mL of anhydrous DMF and stirring at 0°. The precipitate complex $CdCl_2$, 1.5 DMF was filtered of and washed with CCl_4 (yield 96 %).

The $CdCl_2$ -1.5 DMF complex (21 mmol) is added to 1.14 g (30 mmol) of $NaBH_4$ in 150 mL of anhydrous CH_3CN and 7.5 mL of HMPA.

The suspension is stirred at - 5°C for 5 min, and then a solution of acyl chloride, 5.05g (30 mmol) in 10 mL of CH_3CN, was added in one portion. After 3 min the mixture was diluted with water (10 mL) and acidified with HCl 10 %.

The organic solvents were removed under reduced pression. The residue was extracted with Et_2O, the extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed over a column of silica gel with 15:85 Ethylacetate / Petroleum ether as eluant to afford the requisite aldehyde 4c ; (yield: 48 %) ; liq , n^{19}= 1.527; IR (neat) : 1725 cm^{-1} ; ^1H

NMR (60 MHz , $CDCl_3$) : δ (ppm) 3.4 (d, 2H, J = 2.5 Hz), 3.6 (s, 3H), 6.95 (s, 5H), 9.50 (t, 1H, J= 2.5 Hz).

3,5-hexadienoic acid derivatives General procedure :

A solution of dimethyl-3-methylglutaconate 1 (10 mmol) and aldehyde 5 (10 mmol) in dry ether or THF (15 mL) was added dropwise to a stirred suspension of MeONa (11 mmol) in ether or THF (50 mL) at - 20°C under N_2 atmosphere. The temperature is allowed to rise to 20°C and stirring was continued for 2 hours. Water (100 mL) is then added and the mixture was extracted with ether (2 x 50 mL), the aqueous solution was acidified to pH 1 with 10 % hydrochloric acid. The filtered precipitate was recrystallized from (Ethylacetate/Petroleum ether 1:4) to give pure 7a-f (yields in Table).

7a : m.p. 91-92°C ; IR (KBr) : 3300-2700 , 1725 , 1700 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) : δ (ppm) 2.05 (s, 3H), 3.25 (s, 2H), 3.85 (s, 3H), 6.4 (d, 1H, J = 16 Hz), 6.9 (d, 1H, J = 16 Hz), 7.35 (m, 5H), 9.75 (br.s, 1H).

7b : m.p. 118-119°C; IR (KBr) : 3300-2700, 1725, 1700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ (ppm) 2.01 (s, 3H), 2.27 (s, 3H), 3.21 (s, 2H), 3.80 (s, 3H), 6.4 (d, 1H, J = 16 Hz), 6.85 (d, 1H, J=16 Hz) , 7.05 (d, 2H, J = 8 Hz), 7.25 (d, 2H, J = 8 Hz), 10.1 (br.s,1H).

7c : m.p. 140-141°C ; IR (KBr): 3300-2700,1730,1700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ (ppm) 2.07 (s, 3H), 3.27 (s, 2H), 3.81 (s, 3H), 3.87 (s, 3H), 6.4 (d, 1H, J = 16 Hz), 6.8 (d, 1H, J = 16 Hz), 6.85 (d, 2H, J = 8 Hz), 7.30 (d, 2H, J = 8 Hz), 10.20 (br.s, 1H).

7d : m.p. 142-143°C ; IR (KBr) : 3300-2700, 1720, 1700 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ (ppm) 2.01 (s, 3H), 3.22 (s. 2H), 3.79 (s, 3H), 6.4 (d, 1H, J = 16 Hz), 6.8 (d, 1H, J = 16 Hz), 7.2 (m, 4H), 10.15 (br.s, 1H).

7e : m.p. 115-116°C ; IR (KBr) : 3300-2700, 1725 , 1700 cm^{-1} ; ^1H NMR (80 MHz, $CDCl_3$) : δ (ppm) 2.0 (s, 6H), 3.42 (s, 2H), 3.70 (s, 3H), 6.3 (s, 1H), 7.15-7.5 (m, 5H), 9.5 (br.s, 1H).

7f : m.p. 111-112°C ; IR (KBr): 3300-2700, 1720, 1700 cm^{-1} ; ^1H N[illegible] (80 MHz, $CDCl_3$: δ (ppm) 1.90 (s, 3H), 3.25 (s, 5H), 6.54 (s, 1H), 6.95-7.30 (m, 10H), 10.4 (br.s, 1H).

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