Acylation Reaction of γ,β-Unsaturated β-Keto Esters and of Ethyl Hydrogen Malonate. Synthesis of 6-Alkenyl-5-ethoxycarbonyl-2,3-dihydro-4*H*-pyran-4-ones and 4,5-Dioxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyran Derivatives

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The syntheses of 6-alkenyl-5-ethoxycarbonyl-2,3-dihydro-4*H*-pyran-4-one derivatives by acylation of γ,β-unsaturated β-keto esters or by diacylation of ethyl hydrogen malonate with α,β-unsaturated acyl chlorides are described. These compounds were converted to 4,5-dioxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyran derivatives.

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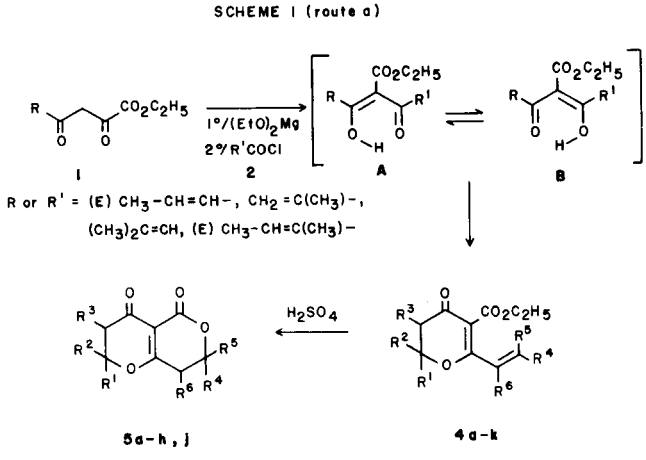
The preparation of 5-ethoxycarbonyl-2,3-dihydro-4*H*-pyran-4-one derivatives by condensing an appropriate β-keto ester with α,β-unsaturated acyl chlorides has been described by us previously [1,2]. Due to the utility of this class of heterocycle in synthetic chemistry [3,4], we describe here the results of our work directed to the synthesis of the hitherto unknown 5-ethoxycarbonyl-2,3-dihydro-4*H*-pyran-4-ones **4a-k**, bearing an alkenyl substituent at the 6 position and their subsequent transformation into 4,5-dioxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyran derivatives **5a-k**.

Acylation of the magnesium salts of γ,δ-unsaturated 2-keto esters **1**, in toluene/acetonitrile, with the alkenoyl acyl chlorides **2**, afforded the dihydropyrone derivatives *via* nucleophilic addition of an enolic hydroxy group to an ole-

SCHEME I (route a)



	R¹	R²	R³	R⁴	R⁵	R⁶
a	Me	H	H	Me	H	H
b	H	H	Me	H	H	Me
c	Me	Me	H	Me	Me	H
d	Me	H	H	H	H	Me
e	H	H	Me	Me	H	H
f	Me	Me	H	Me	H	H
g	Me	H	H	Me	Me	H
h	Me	Me	H	H	H	Me
i	H	H	Me	Me	Me	H
j	Me	H	Me	Me	H	H
k	Me	H	H	Me	H	Me

SCHEME II

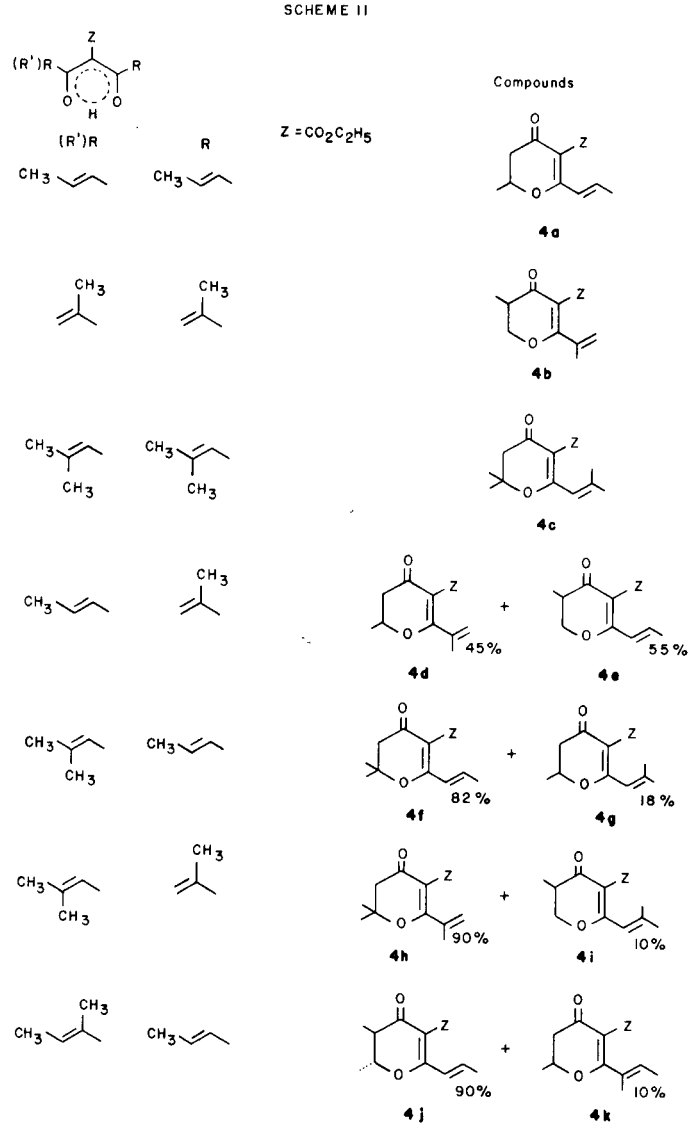


Table 1

Physical Data for Compounds **4** and **5**

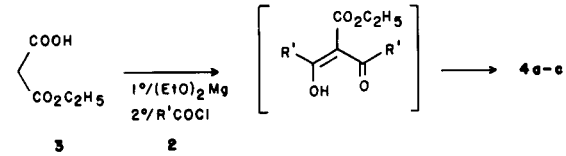
Compound No.	Yield %	n_D^{17} or Mp °C	Molecular Formula	Analyses % (Calcd./Found) C	H	IR (Chloroform) νC=O cm^{-1}	UV (Ethanol) λ max nm (ε)
4a	50 [a]	1.5340	$C_{12}H_{16}O_4$	64.27	7.19	1730	295 (17000)
	82 [b]			64.04	7.19	1680	240 (8500)
4b	70 [a]	1.5120	$C_{12}H_{16}O_4$	64.27	7.19	1735	276 (8200)
	61 [b]			64.11	7.22	1680	
4c	65 [a]	1.5180	$C_{14}H_{20}O_4$	66.64	7.99	1735	306 (17600)
	68 [b]			66.44	7.87	1680	250 (7000)
4d	20 [a]	1.7290	$C_{12}H_{16}O_4$	64.27	7.19	1735	272 (11100)
				64.67	7.09 [c]	1675	
4e	30 [a]	1.5350	$C_{12}H_{16}O_4$	64.27	7.19	1735	296 (16300)
				64.67	7.09 [c]	1680	240 (8000)
4f	45 [a]	1.5210	$C_{13}H_{18}O_4$	65.53	7.61	1735	300 (14000)
				65.63	7.57 [c]	1680	240 (7500)
4g	10 [a]	65-70	$C_{13}H_{18}O_4$	65.53	7.61	1735	303 (14100)
				65.63	7.57 [c]	1680	252 (6000)
4h	60 [a]	1.5040	$C_{13}H_{18}O_4$	65.53	7.61	1740	286 (9000)
				65.11	7.68	1680	
4j	50 [a]	1.5224	$C_{13}H_{18}O_4$	65.53	7.61	1725	296 (15500)
				65.33	7.42	1675	240 (8300)
5a	65 [d]	150-152	$C_{10}H_{12}O_4$	61.21	6.17	1740	259 (10000)
	46 [e]	[f]		61.43	6.07	1680	
5b	71 [d]	118-120	$C_{10}H_{12}O_4$	61.21	6.17	1750	258 (10000)
	31 [e]			61.06	6.02	1680	
5c	84 [d]	166-167	$C_{12}H_{16}O_4$	64.27	7.19	1745	261 (9800)
	43 [e]			64.54	7.11	1675	
5d	45 [d]	118-120	$C_{10}H_{12}O_4$	61.21	6.17	1740	260 (11200)
				61.18	6.15	1675	
5e	67 [d]	204-205 dec	$C_{10}H_{12}O_4$	61.21	6.17	1750	259 (10000)
				61.05	6.05	1680	
5f	60 [d]	146-147	$C_{11}H_{14}O_4$	62.84	6.71	1750	260 (9700)
				62.79	6.65	1680	
5g	79 [d]	185-186 dec	$C_{11}H_{14}O_4$	62.84	6.71	1750	259 (11000)
				62.73	6.83	1680	
5h	81 [d]	127-128	$C_{11}H_{14}O_4$	62.84	6.71	1755	260 (12300)
				62.96	6.69	1680	
5j	71 [d]	206-208	$C_{11}H_{14}O_4$	62.84	6.71	1745	262 (10000)
				62.96	6.69	1675	

[a] Yield after column chromatography, route a. [b] Yield after distillation route b. [c] Analysis of the mixture of **4d** + **4e** or **4f** + **4g**. [d] Yield based from **4** according to route a. [e] Yield based from ethyl hydrogen malonate according to route b. [f] Lit mp 125-128° [7].

finic carbon atom from the intermediate ethyl diacryloylacetates. The diacyl groups of these intermediates could be identical or different, depending on the choice of the starting material (Scheme I, route a). In the case of two identical acyl residues (R = R'), the compounds **4a-c** were obtained. In the case of two different alkenoyl residues, the open chain intermediate can exist in two tautomeric forms **A** and **B**, consequently, there is formation of a mixture of two isomeric dihydropyrones. The double bond bearing two methyl groups has been found more receptive to the conjugate addition (compounds **4f**, **4h** and **4j**) (82-90%) than the one with only one methyl substituent (compounds **4g**, **4i** and **4k**) (18-10%). The isomeric ratio was easily determined by ^1H nmr analysis. Representative results are summarized in the Scheme II. Pure compounds were obtained by column chromatography, with the exception of **4i** and **4k**.

The synthesis of compounds **4a-c** was also achieved by the diacylation reaction of the ethoxymagnesio enolate of ethyl hydrogen malonate **3** by the substituted acryloyl

Scheme III (route b)



3 2

R' = (E) CH_3-CH=CH-, CH_2=C(CH_3)-, (CH_3)$_2$C=CH-

Table 2

Proton Magnetic Resonance Parameters of Compounds **4** and **5**

Compound No.	Chemical shift [a]
4a	1.36 (t, 3H, J = 7 Hz), 1.51 (d, 3H, J = 6 Hz), 1.93 (dd, 3H, J = 6 Hz, 1 Hz), 2.52 (d, 2H, J = 8 Hz), 4.33 (q, 2H, J = 7 Hz), 4.60 (m, 1H), 6.40 (dq, 1H, J = 16 Hz, 1 Hz) and 6.88 (dq, 1H, J = 16 Hz, 6 Hz) [b]
4b	1.15 (d, 3H, J = 7 Hz), 1.28 (t, 3H, J = 7 Hz), 1.98 (s, 3H), 2.67 (m, 1H), 4.16 (dd, 1H, J = 11 Hz, 11 Hz) [c] and 4.57 (dd, 1H, J = 11 Hz, 5 Hz) [d], 4.23 (q, 2H, J = 7 Hz), 5.37 (m, 1H), 5.53 (s, 1H)
4c	1.32 (t, 3H, J = 7 Hz), 1.51 (s, 6H), 1.95 (s, 3H), 2.08 (s, 3H), 2.56 (s, 2H), 4.30 (q, 2H, J = 7 Hz), 6.11 (m, 1H)
4d	1.27 (t, 3H, J = 7 Hz), 1.51 (d, 3H, J = 7 Hz), 1.98 (s, 3H), 2.52 (m, 2H), 4.23 (q, 2H, J = 7 Hz), 4.63 (m, 1H), 5.36 (m, 1H), 5.51 (s, 1H)
4e	1.16 (d, 3H, J = 7 Hz), 1.36 (t, 3H, J = 7 Hz), 1.93 (d, 3H, J = 6 Hz), 2.65 (m, 1H), 4.12 (dd, 1H, J = 11 Hz, 11 Hz) [c] and 4.53 (dd, 1H, J = 11 Hz, 5 Hz) [d], 4.32 (q, 2H, J = 7 Hz), 6.35 (dq, 1H, J = 16 Hz, 1 Hz) and 6.82 (dq, 1H, J = 16 Hz, 6 Hz) [b]
4f	1.35 (t, 3H, J = 7 Hz), 1.47 (s, 6H), 1.93 (d, 3H, J = 6 Hz), 2.57 (s, 2H), 4.32 (q, 2H, J = 7 Hz), 6.43 (dq, 1H, J = 16 Hz, 1 Hz) and 6.83 (dq, 1H, J = 16 Hz, 6 Hz) [b]
4g	1.33 (t, 3H, J = 7 Hz), 1.52 (d, 3H, J = 7 Hz), 1.95 (s, 3H), 2.08 (s, 3H), 2.52 (d, 2H, J = 8 Hz), 4.33 (q, 2H, J = 7 Hz), 4.65 (m, 1H), 6.10 (s, 1H)
4h	1.27 (t, 3H, J = 7 Hz), 1.50 (s, 6H), 1.96 (s, 3H), 2.57 (s, 2H), 4.22 (q, 2H, J = 7 Hz), 5.34 (m, 1H), 5.46 (s, 1H)
4j [e]	1.13 and 1.22 (2d, 3H, J = 7 Hz), 1.37 (t, 3H, J = 7 Hz), 1.52 and 1.41 (2d, 3H, J = 7 Hz), 1.93 (d, 3H, J = 6 Hz), 2.07-2.65 (m, 1H), 4.00-4.47 (m, 2.8H), and 4.65 (m, 0.2H), 6.35 (dq, 1H, J = 16 Hz, 1 Hz) and 6.82 (dq, 1H, J = 16 Hz, 6 Hz) [b]
5a	1.456 and 1.459 (2d, 3H, J = 6.0 Hz), 1.540 and 1.531 (2d, 3H, J = 6.5 Hz), 2.53-2.74 (m, 2H), 4.535 (m, 1H), 4.744 and 4.837 (2m, 1H)
5b	1.171 (d, 3H, J = 6.9 Hz), 1.284 and 1.309 (2d, 3H, J = 7.3 Hz), 2.76 (m, 1H), 2.87 (m, 1H), 3.99-4.05 (m, 1H), 4.24-4.38 (m, 2H), 4.64-4.70 (m, 1H)
5c	1.50 (s, 6H), 1.55 (s, 6H), 2.70 (s, 4H)
5d [e]	1.269 and 1.332 (2d, 3H, J = 7.2 Hz), 1.547 and 1.552 (2d, 3H, J = 6.0 Hz), 2.60-2.77 (m, 2H), 2.910 and 2.794 (2m, 1H), 3.97-4.07 (m, 1H), 4.28-4.39 (m, 1H), 4.72-4.83 (m, 1H)
5f	1.45 (d, 3H, J = 6 Hz), 1.51 (s, 3H), 1.56 (s, 3H), 2.42-2.97 (m, 4H), 4.58 (m, 1H)
5g	1.51 (s, 6H), 1.57 (d, 3H, J = 7 Hz), 2.32-2.97 (m, 4H), 4.82 (m, 1H)
5h	1.31 (d, 3H, J = 7 Hz), 1.52 (s, 3H), 1.56 (s, 3H), 2.70 (s, 2H), 2.83 (m, 1H), 4.10 (dd, 1H, J = 11 Hz, 6 Hz) and 4.45 (dd, 1H, J = 11 Hz, 5 Hz) [d]
5j [e]	1.149 and 1.158 (2d, 3H, J = 7.5 Hz), 1.444 and 1.450 (2d, 3H, J = 7.0 Hz), 1.537 and 1.528 (2d, 3H, J = 7.0 Hz), 2.43-2.49 (m, 1H), 2.50-2.73 (m, 2H), 4.381 and 4.454 (2m, 1H), 4.48-4.58 (m, 1H)

[a] δ ppm from TMS in deuteriochloroform. The spectra were recorded on a 350 MHz Cameca spectrometer for the compounds **5a,b,d,e** and **j** and on a 80 MHz Brucker spectrometer for the other compounds. [b] AB part of ABX_3 system, in first order treatmeent. [c] Partially masked by th methylene protons of the ethoxycarbonyl group. [d] AB part of ABX system, in first order treatment. [e] Mixture of two stereoisomers. The first value of the two assignments represents the more intense peak (major isomer). Isomeric ratios determined by ^{1}H-nmr: **4j** (80/20), **5a** (60/40) **5b** (55/45), **5d** (65/35), **5j** (70/30).

chlorides **2** (Scheme III, route b). It was known that this enolate underwent diacylation by saturated acyl chlorides [5,6]. The efficacity and reproductibility of this diacylation reaction, using alkenoic acyl chlorides, were found dependent of the solvent reaction and the nature of the acyl chloride (see Experimental).

Upon treatment with concentrated sulfuric acid, at room temperature, the alkenyldihydropyrones **4a-h** and **4j** were easily converted to 4,5-dioxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyrans **5a-h** and **5j**. Although the compounds 2,7; 3,8; 2,8; 3,7-dimethyl (respectively **5a, 5b, 5d** and **5e**) and 2,3,7-trimethyl **5j** tetrahydropyranopyrans appeared homogeneous by tlc, their 350 MHz ^{1}H nmr spectra revealed the presence of a mixture of inseparable *cis* and *trans* isomers.

Compound **5a** (2,7-dimethyl) was precedently described [7], while no isomeric mixture was detected. We repeated the original preparation involving the condensation of crotonoyl chloride upon 2,4-dioxo-5-methyl-5,6-dihydro-2*H*,4*H*-pyran in the presence of titanium(IV) chloride. All physical data an nmr examination indicated the material to be identical with the *cis/trans* mixture prepared by our method. However, the melting point observed was appreciably higher than the one recorded.

EXPERIMENTAL

All melting points were determined on a Kofler apparatus. The infrared spectra were recorded on a Beckman Acculab 2 spectrometer. The ultraviolet spectra were obtained on a Beckman DB spectrometer in ethanol. Elemental analyses were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

γ,δ-Unsaturated β-Keto Esters **1**.

They are prepared as previously described; ethyl *(E)*-3-oxo-4-hexenoate [8], ethyl 4-methyl-3-oxo-4-pentenoate [8], ethyl 5-methyl-3-oxo-4-hexenoate [9], ethyl *(E)*-4-methyl-3-oxo-4-hexenoate [10].

6-Alkenyl-5-ethoxycarbonyl-2,3-dihydro-4*H*-pyran-4-ones [4]. General Procedure. Route a.

To a solution of γ,δ-unsaturated β-keto ester **1** (0.05 mole) in dry toluene (75 ml) was added (5.7 g) (0.05 mole) of magnesium ethylate. The mixture was magnetically stirred and heated to reflux for 2 hours. After cooling to 0-5° in an ice bath, the resultant mixture was diluted with acetonitrile (50 ml) and a solution of the γ,β- unsaturated acyl chloride **2** (0.055 mole) in acetonitrile (25 ml) was added dropwise with vigourous stirring. After addition was complete, the reaction mixture was stirred at room temperature for two hours. The mixture was then poured on to cold 10% sulfuric acid solution (100 ml). The organic layer was separated and the aqueous layer was extracted with ether (50 ml). The combined extracts were washed twice with saturated aqueous sodium bicarbonate (2 × 30 ml) and water (50 ml), then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was distilled at reduced pressure (120-150°/1 torr). The crude products were purified and the isomeric mixtures were separated by chromatography on silica-gel using ether as eluent. In the case of a mixture, the major isomer **4e, 4f, 4h, 4j** was first eluted and then **4d** or **4g**; the minor compounds **4i** and **4k** were not obtained in pure state. Yields and physical data are summarized in the Tables 1 and 2.

6-Alkenyl-5-ethoxycarbonyl-2,3-dihydro-4*H*-pyran-4-ones (**4a-c**). Route b.

To a solution of freshly distilled ethyl hydrogen malonate **3** (6.6 g, 0.05 mole) in dry toluene (100 ml) was added 11.4 g (0.1 mole) of magnesium ethylate. The mixture was magnetically stirred and heated to reflux for 2 hours. The solvent was then rotary-evaporated to dryness. The residue (the ethoxymagnesio enolate of **3**) was diluted with 250 ml of the following solvents: methylene chloride:tetrahydrofuran (3:2) in the case of **4a**; methylene chloride in the case of **4b** or tetrahydrofuran in the case of **4c**. The resultant mixture was cooled to 0-5° with an ice bath and a solution of the β-unsaturated acyl chloride **2** (0.15 mole) in 50 ml of the appropriate solvent was added dropwise with stirring. After 1 hour, the ice bath was removed and the reaction mixture was stirred overnight at room temperature (in the case of **4a**) or heated to reflux for 3 hours (in the case of **4b** and **4c**). The reaction mixture was then poured on to cold 10% hydrochloric acid (200 ml) and the aqueous layer was extracted with methylene chloride. The combined extracts were worked up as described above. The solvent was then removed and the remaining residue was distilled at reduced pressure (120-150°/1 mm) to give crude **4a** (9.2 g, 82%), **4b** (6.8 g, 61%) or **4c** (8.5 g, 68%). These products can be used without further purification to prepare compounds **5a-c**.

4,5-Dioxo-2,3,7,8-tetrahydro-4*H*,5*H*-pyrano[4,3-*b*]pyran Derivatives (**5**). General Procedure.

6-Alkenyl-5-ethoxycarbonyl-2,3-dihydro-4*H*-pyran-4-one **4a-h** or **4j** (0.01 mole) was added to concentrated sulfuric acid (20 ml) with cooling and stirring. The mixture was allowed to stand at room temperature for 15 hours. The mixture was then poured on to ice/water (200 g) and extracted with chloroform (4 × 50 ml). The combined extracts were dried with sodium sulfate and evaporated under reduced pressure. The residue was triturated with ether (30 ml) and the white solid product was collected by suction.

Analytical sample was obtained by recrystallization from ethyl acetate except **5e** from ethanol.

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