Condensation of Acetylenic Esters with Ethyl Arylacetates

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Ethyl-substituted phenylpropiolylarylacetates were obtained as the main products of Claisen condensation between ethyl arylpropiolates and ethyl arylacetates in the presence of sodium ethoxide. One anomalous by-product was isolated in the case of ethyl phenylpropiolate and ethyl *m*-chlorophenylacetate. The reaction products were identified on the basis of spectroscopic evidence and elemental analysis.

In a recent paper (*1*), the condensation of ethyl phenylpropiolate with ethyl phenyl-, *p*-tolyl-, *p*-methoxyphenyl-, *p*-chlorophenyl-, and α-napthylacetates was reported to give acetylenic β-keto-esters: ethyl α-(phenyl)-; α-(*p*-tolyl)-; α-(*p*-methoxyphenyl)-; α-(*p*-chlorophenyl)-, and α-(α-naphthyl)-phenyl propiolylacetates, respectively. These β-keto-esters are present in enolic form, characterized by a positive ferric chloride test and by their formation of metal complexes. The reaction pathway could be described as Claisen condensation of the carbanion $\mathrm{Ar\bar{C}H}$—$\mathrm{Co_2Et}$ to ethyl phenylpropiolate with subsequent elimination of the ethanol molecule.

Experimental

Unless otherwise stated, IR spectra were measured with a Unicam SP 200 instrument for solutions in chloroform, ^{1}H NMR spectra with a Varian A-60 D instrument for solutions in deuterated chloroform containing tetramethylsilane as internal standard, and UV spectra with a Unicam SP 800 instrument for solutions in ethanol. Compounds were analyzed at the Max Plank Institute, Ruhr, West Germany. Melting points were determined with a Kofler hot-stage apparatus. Elemental analyses in agreement with theoretical values were obtained and submitted for review.

In each condensation, equimolar amounts of ethyl arylacetate and ethyl arylpropiolate were added successively to a suspension of sodium ethoxide in dry ether. The mixture was kept at room temperature for three days and then poured into water (200 ml) and extracted with ether.

Ethyl 2,5-dimethylphenylacetate and ethyl phenylpropiolate. Ethyl 2,5-dimethylphenylacetate (3.3 grams), ethyl phenylpropiolate (3 grams), and sodium ethoxide (1.2 grams) in ether (150 ml) were treated as described. The ethereal extract yielded a reddish oil (1.2 grams), which after treatment with methanol gave the sodium salt of Ia. Acidification of the latter in ether yielded ethyl α-(2,5-dimethylphenyl)phenylpropiolylacetate (Ia) (0.4 gram) which gave pale plates, mp 80° (from methanol).

The alkaline aqueous layer was acidified with dilute sulfuric acid and extracted with ether, and the ethereal solution was shaken with sodium hydrogen carbonate solution. Evaporation of the ethereal layer yielded a further 0.4 gram of the acetylenic β-keto-ester (Ia), mp 80° (from methanol). The sodium hydrogen carbonate washings, after acidification, extraction with ether, and evaporation, yielded phenylpropiolic acid (0.8 gram), mp and mixed mp 136°.

Ethyl o-fluorophenylacetate and ethyl phenylpropiolate. Ethyl *o*-fluorophenylacetate (3.1 grams), ethyl phenylpropiolate (3.0 grams), and sodium ethoxide (1.2 grams) in dry ether (150 ml) were treated as described. The ethereal extract yielded a reddish brown oil (1.5 grams), which after treatment with methanol afforded the sodium salt of Ib. Acidification of the latter and extraction with ether yielded ethyl α-(*o*-fluorophenyl)phenylpropiolylacetate (Ib) (0.3 gram) as colorless plates, mp 56° (from methanol).

The alkaline aqueous layer was acidified with dilute sulfuric acid and extracted with ether. The ethereal solution was shaken with sodium hydrogen carbonate solution. Evaporation of the ethereal layer yielded a further 0.4 gram of the acetylenic β-keto-ester (Ib), mp 56° (from methanol). The sodium hydrogen carbonate washings, after acidification, extraction with ether, and evaporation, gave phenylpropiolic acid (0.5 gram), mp and mixed mp 136°.

Ethyl m-fluorophenylacetate and ethyl phenylpropiolate. Ethyl *m*-fluorophenylacetate (3.1 grams), ethyl phenylpropiolate (3 grams), and sodium ethoxide (1.2 grams) in ether (150 ml) were treated as described. The ethereal extract yielded a reddish oil (2 grams), which after treatment with methanol gave the sodium salt of (Ic). Acidification of the latter and extraction with ether yielded ethyl α-(*m*-fluorophenyl)phenylpropiolylacetate (Ic) (0.4 gram) as colorless plates, mp 62° (from methanol). A further 0.5 gram of the acetylenic (β-keto-ester (Ic) was recovered from the alkaline aqueous layer after acidification with dilute sulfuric acid, extraction with ether, and the removal of phenylpropiolic acid (0.4 gram), mp 136°. It crystallized from methanol as colorless plates, mp 62°.

Ethyl m-chlorophenylacetate and ethyl phenylpropiolate. Ethyl *m*-chlorophenylacetate (3.4 grams), ethyl phenylpropiolate (3 grams), and sodium ethoxide (1.2 grams) in ether (150 ml) were treated as described. The ethereal extract yielded a dark brown oil (4.5 grams) which after treatment with methanol yielded a solid (0.9 gram), which was boiled with ethanol and filtered off. The filtrate, when cooled, deposited crystalline leaflets, mp 76°, which were tentatively proved as 1,5-dicarbethoxy-3-carboxy-3-*m*-chlorophenyl-2,4-diphenyl-1,4-pentadiene (II). The alkaline aqueous layer was acidified with dilute sulfuric acid and extracted with ether. The ethereal solution was shaken with sodium hydrogen carbonate solution. Evaporation of the ethereal layer yielded ethyl α-(*m*-chlorophenyl)phenylpropiolylacetate (Id) (0.7 gram), mp 70°, as colorless plates (from methanol). The sodium hydrogen carbonate washings, after acidification, extraction with ether, and evaporation, yielded phenylpropiolic acid (0.6 gram), mp and mixed mp 136°.

Ethyl phenylacetate and ethyl o-chlorophenylpropiolate. Ethyl phenylacetate (2.8 grams), ethyl *o*-chlorophenylpropiolate (3.6 grams), and sodium ethoxide (1.2 grams) in ether (150 ml) were treated as described. The ethereal extract gave a reddish oil (2.5 grams) from which, after treating with methanol and cooling, no solid material could be isolated.

The alkaline aqueous solution was acidified with dilute sulfuric acid and extracted with ether, and the ethereal solution was then shaken with sodium hydrogen carbonate solution. Evaporation of the ethereal layer yielded pale plates of ethyl α-(*o*-chlorophenylpropiolyl)phenylacetate (Ie) (0.9 gram), mp 99–100° (from ethanol). The sodium hydrogen carbonate washings, after acidification, extraction with ether, and evaporation, gave *o*-chlorophenylpropiolic acid (0.7 gram), mp and mixed mp 130°.

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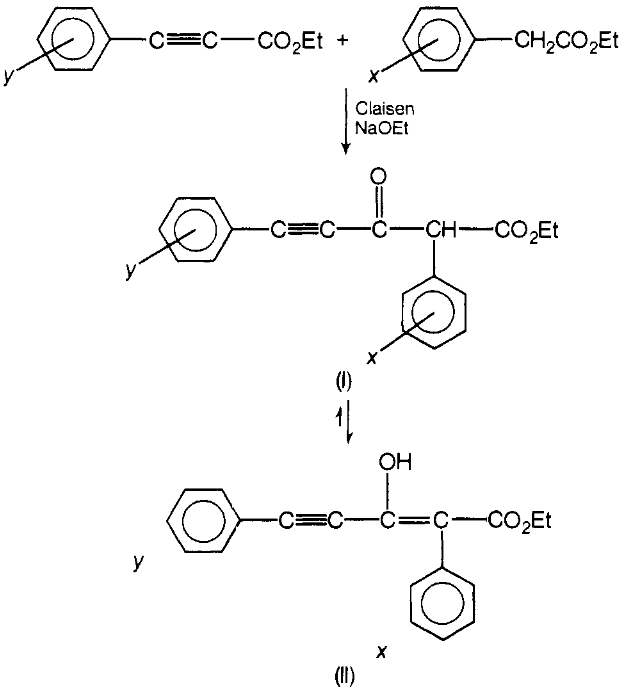
Ethyl phenylacetate and ethyl p-methoxyphenylpropiolate. Ethyl phenylacetate (2.8 grams), ethyl *p*-methoxyphenylpropiolate (3.5 grams), and sodium ethoxide (1.2 grams) in ether (150 ml) were treated as described. The ethereal extract yielded a reddish oil (3 grams), which after treatment with a few drops of methanol, gave the sodium salt of If. Acidification of the latter and extraction with ether yielded ethyl α-(*p*-methoxyphenylpropiolyl)phenylacetate (If) (0.6 gram) as pale crystalline leaflets, mp 104° (from methanol plus a few drops of petroleum ether 60–80°).

The alkaline aqueous layer was acidified with dilute sulfuric acid and extracted with ether, and the ethereal extract was then shaken with sodium hydrogen carbonate solution. Evaporation of the ethereal layer afforded a further 0.8 gram of the acetylenic β-keto-ester (If), mp 104° (from methanol). The sodium hydrogen carbonate washings, after acidification, extraction with ether, and evaporation, yielded *p*-methoxyphenylpropiolic acid (0.6 gram), mp and mixed mp 139°.

Results and Discussion

Ethyl α-(aryl)-arylpropiolylacetates (I) were obtained from the reaction of ethyl arylacetates and ethyl arylpropiolates in the presence of sodium ethoxide. Studies of the condensation products showed that the reaction proceeded through Claisen condensation of the carbanion ($Ar—\bar{C}H—CO_2Et$) to the propiolic ester followed by elimination of the ethanol molecule as shown in Scheme 1:

Scheme 1



	y	x		y	x
a:	H	2,5-DiMe	d:	H	*m*-Chloro
b:	H	*o*-Fluoro	e:	*o*-Chloro	H
c:	H	*m*-Fluoro	f:	*p*-Methoxy	H

These reaction products were identified by means of spectral and elemental analysis. The IR spectral data (Table I) showed a broad absorption between 2500–3500 cm^{-1} due to the OH group, and another absorption appeared at 1645 cm^{-1}, characteristic of the chelated β-keto-ester system (*2*). Also, a sharp band near 2230 cm^{-1} indicated the presence of an acetylenic linkage. These acetylenic β-keto-esters almost exist in the enol form (II), and the presence of enolic hydrogen was supported by NMR spectral data (Table I). A sharp signal occurred downfield at τ −2.5, which is unusual for this type of proton (*3*), and exchangeable with deuterated water. The UV spectral data (Table II) also confirmed the outlined structures. It showed a red shift and a hyperchromic effect (*4*) in alkaline and nonhydroxylic solvent ($CHCl_3$), possibly due to the charged species formed under these conditions.

Table I. IR and NMR Spectral Data of Ethyl α-(Arylpropiolyl)arylacetate (I)

Compound	IR ($CHCL_3$)			NMR ($CDCl_3$),[a] protons
	Cm^{-1}	ν	τ	
Ia	2500–3500	OH	2.75	$Ar\underline{H}$
	2240	C≡C	−2.47 (s)	$C:\bar{C}(O\underline{H})^b$
	1640	C═C	5.71 (q)	OCH_2
			7.73 (d)	$Ar(\underline{Me})_2$
			8.81 (t)	CH_2CH_3
Ib	2500–3500	OH	2.65	$Ar\underline{H}$
	2250	C≡C	−2.58 (s)	$C:\bar{C}(OH)^b$
	1642	C═C	5.67 (q)	OCH_2
			8.77 (t)	CH_2CH_3
Ic	2500–3600	OH	2.68	$Ar\underline{H}$
	2235	C≡C	−2.51 (s)	$C:\bar{C}(O\underline{H})^b$
	1640	C═C	5.69 (q)	OCH_2
			8.78 (t)	CH_2CH_3
Id	2500–3400	OH	2.6	$Ar\underline{H}$
	2235	C≡C	−2.58 (s)	$C:\bar{C}(O\underline{H})^b$
	1645	C═C	5.67 (q)	OCH_2
			8.76 (t)	CH_2CH_3
Ie	2500–3300	OH	2.62	$Ar\underline{H}$
	2250	C≡C	−2.56	$C:\bar{C}(O\underline{H})^b$
	1640	C═C	5.67 (q)	OCH_2
			8.77 (t)	CH_2CH_3
If	2600–3400	OH	2.54–3.24	$Ar\underline{H}$
	2220	C≡C	−2.58 (s)	$C:\bar{C}(O\underline{H})^b$
	1640	C═C	5.70 (q)	OCH_2
			6.2 (s)	$ArO\underline{Me}$
			8.78 (t)	CH_2CH_3

[a] ArH, appeared as multiplet. [b] Exchanged with deuterated water.

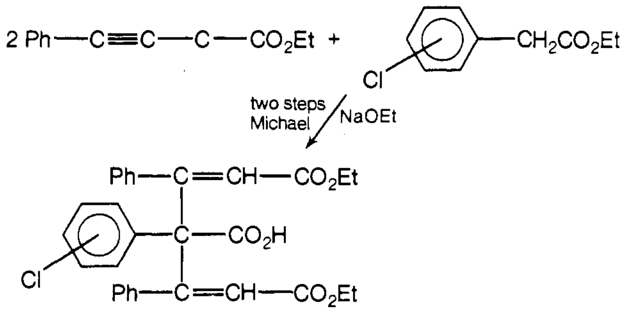
Table II. UV Light Absorption Spectral Data of Ethyl α-(Arylpropiolyl)arylacetate (I)

Compound	EtOH		$CHCl_3$		0.1*N* NaOH	
	λ_{max}	Log ϵ_{max}	λ_{max}	Log ϵ_{max}	λ_{max}	Log ϵ_{max}
Ia	314	4.25	317	4.11	332	3.90
	218	4.10	249	3.43	250	3.96
					222	3.86
Ib	315	4.31	318	4.18	330	4.18
	272 (sh)	3.94	250	3.67	250	4.20
	245 (sh)	3.80			222	4.01
	221	4.00				
Ic	318	4.19	321	4.23	331	4.20
	247	3.85	249	3.83	251	4.24
	223	3.94			224	4.08
Id	319	4.16	323	4.21	334	3.69
	242	3.89	251	3.87	250	3.77
	218	4.08			221	3.67
Ie	322	4.13	327	4.07	338	3.82
	282 (sh)	3.94	248	3.65	255	3.91
	230	4.05			223	3.87
	217	4.05				
If	331	4.33	337	4.51	338	3.79
	254 (sh)	3.76	300 (sh)	4.16	258	3.75
	230	3.94	248 (sh)	3.95	222	3.61
			253	3.97		

The existence of β-keto-ester in the enolic form was also supported by a positive ferric chloride test and by their formation of metal complexes.

In the case of the condensation of ethyl phenylpropiolate with ethyl *m*-chlorophenylacetate, another more crystalline compound (II) was isolated from the neutral extract. Spectral and elemental analysis agreed with the structure (II) which is the outcome of double Michael addition between 1 mole of *m*-chlorophenylacetate and 2 moles of ethyl phenylpropiolate, with subsequent hydrolysis of the acetate group as shown in Scheme 2:

Scheme 2



(II)

The presence of the carboxy-group was supported by the sodium bicarbonate test. More evidence for structure (II) was obtained from spectral data. The UV absorption spectrum showed a red shift in sodium hydroxide solution, whereas the IR spectrum showed the absence of acetylenic linkage, thus supporting the mechanism of the reaction to proceed through Michael addition. The NMR spectrum also favored the above structure. Two AB quartets appeared at 5.96 and 6.4 τ integrated to four protons. The corresponding six proton triplets appeared at 9.32 τ, thus confirming two carbethoxy groups in the molecule. The ethylenic protons of the two cinnamate fragments overlapped by the aromatic protons and showed a complex pattern between 2.52–2.9 τ. The one proton resonance signal at -1.86 τ (exchangeable with heavy water) was attributed to the carboxylic acid proton. The formation of such a compound (II) could be interpreted by certain factors including the nature of the substituent and the bulk of the molecule.

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Condensation of Acetylenic Esters with Arylacetamides

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14,5-Diaryl-1,5-dihydro-2H,6H-pyridine-2,6-dione was prepared by condensation of arylpropiolic esters with arylacetamides in the presence of powdered sodium and boiling benzene. Some of the *N*-derivatives of the condensation products were also prepared. The various structures were confirmed spectroscopically and by elemental analysis.

The condensation between ethyl phenylpropiolate and phenylacetamide (*5*) or *P*-substituted phenylacetamides (*1*) has been reported. The condensation product was identified as 4,5-diaryl-1,5-dihydro-2H,6H-pyridine-2,6-dione and not phenylpropiolyl phenylacetamide as described by Ruhemann (*9*). The reaction proceeded either by Claisen condensation of the anion $PhCH_2CO\bar{N}H$ or Michael addition of the carbanion $Ph\bar{C}HCONH_2$ to the propiolic ester with subsequent cyclization. The Claisen route seems more likely by analogy to the condensation of benzyl cyanide (*2*) or ethyl phenylacetates (*3*) with ethyl phenylpropiolate.

Experimental

Unless otherwise stated, IR spectra were measured with a Unicam SP 200 instrument for solutions in chloroform, ^1H NMR spectra with a Varian A-60 D instrument for solution in deuterated chloroform containing tetramethylsilane as internal standard, and UV spectra with a Unicam SP 800 instrument for solutions in ethanol. Microanalytical samples were analyzed in West Germany by Max Plank Institute, Ruhr. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses in agreement with theoretical values were obtained and submitted for review.

Condensation of arylacetamides with arylpropiolic esters. Arylacetamide (1 mole) and powdered sodium (1 gram atm) in dry benzene (150 ml) were kept under reflux for 22 hr. Arylpropiolic ester (1 mole) was then added, and heating under reflux was continued for a further 2 hr. The mixture was poured into water (200 ml), and the benzene layer was separated. The alkaline aqueous layer was acidified with dilute sulfuric acid, extracted with ether, and the ethereal extracts were shaken with sodium hydrogen carbonate solution. The nonacidic ethereal and benzene extracts were combined together and dried by sodium sulfate. The sodium hydrogen carbonate washings after acidification, extraction with ether, and evaporation gave the corresponding arylpropiolic acid.

2,5-Dimethylphenylacetamide and ethyl phenylpropiolate. 2,5-Dimethylphenylacetamide (2.8 grams), ethyl phenylpropiolate (3 grams), and powdered sodium (0.4 gram) in benzene (150 ml) were treated as described. The combined benzene–ether extracts after evaporation gave a solid (2.4

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