Reactions of Ethyl Cinnamates with Arylacetamides

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Reactions of ethyl cinnamates with arylacetamides gave the corresponding 2,6-diketo-3,4-diarylpiperidine (**1a-o**) in addition to the corresponding cinnamides (**2a-o**) and arylacetates (**3a-o**). The latter two are formed from the intermediates of the Claisen condensation of the reactants. On the other hand and contrary to the above results, condensation of *p*-methoxycinnamate with arylacetamides gave only *p*-methoxycinnamide in quantitative yields with the corresponding arylacetates.

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Koelsch (1) and Cook (2) synthesized γ-cyanoesters by Michael condensation of benzylcyanide and ethylcinnamates. It was shown that the hydrolysis of these γ-cyanoesters gave the corresponding cyanoacids, which were subsequently hydrolyzed with conc. H_2SO_4 to γ-amido-β,γ-diphenylbutyric acid. The latter gave 2,6-diketo-3,4-diphenylpiperidine upon heating above the melting point. Mayer and Hauser (3) reported the synthesis of this compound by condensing phenylacetamide and ethyl cinnamate using sodium amide as a catalyst. Recently, a series of 2,6-diketopiperidines were prepared from the condensation of cinnamaldehydes with arylacetamides (4).

Condensation of ethyl cinnamates with arylacetamides in the presence of powdered sodium gave the corresponding 2,6-diketo-3,4-diarylpiperidine in addition to the corresponding substituted cinnamides and arylacetates. Contrary to these isolated products, the *p*-methoxyethylcinnamates when condensed with arylacetamides gave only *p*-methoxycinnamide and no imido compound could be isolated.

The reaction pathway could be interpreted as a Claisen condensation of the anion derived from arylacetamides with the cinnamic esters, followed by subsequent cyclization (Scheme 1), as has been reported for other cases (5-8). The formation of the cinnamide could be explained only if the addition took place by a Claisen pathway, followed by the nucleophilic attack of ethoxide ion on the carbonyl carbon atom of the amide residue in the corresponding intermediate. Subsequent cleavage of the N-C bond could then result in formation of the corresponding cinnamide and ethyl phenylacetate. This gives further support to the proposed reaction pathway.

The non-formation of the 2,6-diketo-3,4-diarylpiperidine in the case of ethyl *p*-methoxycinnamate could be due to the mesomeric effect which would make the contributing resonance structure impossible to cyclize to give the corresponding imido compounds (Scheme 2).

The structure of the reaction products was deduced

Table I

2,6-Diketo-3,4-diarylpiperidines

					Analysis (%)							
					Calcd.				Found			
Compound	X	Y	M.p.°C	Formula	C	H	N	Halogen	C	H	N	Halogen
1a	H	H	225	$C_{17}H_{15}NO_2$	77.0	5.6	5.3		76.8	5.9	5.5	
1b	H	*o*-F	208	$C_{17}H_{14}FNO_2$	72.1	4.9	4.9	6.7	72.2	4.7	4.8	6.4
1c	H	*m*-F	216	$C_{17}H_{14}FNO_2$	72.1	4.9	4.9	6.7	72.2	4.8	4.7	6.5
1d	H	*m*-Cl	194	$C_{17}H_{14}ClNO_2$	68.1	4.7	4.7	11.8	68.3	4.5	4.4	11.7
1e	H	*p*-F	222	$C_{17}H_{14}ClNO_2$	72.1	4.9	4.9	6.7	71.9	4.8	4.8	6.6
1f	*p*-Cl	H	204	$C_{17}H_{14}ClNO_2$	68.1	4.7	4.7	11.8	68.3	4.7	4.7	11.6
1g	*p*-Cl	*o*-F	194	$C_{17}H_{13}ClFNO_2$	64.3	4.1	4.4	6.0 F	64.4	4.3	4.6	6.8 F
								11.2 Cl				11.3 Cl
1h	*p*-Cl	*m*-F	200	$C_{17}H_{13}ClFNO_2$	64.3	4.1	4.4	6.0 F	64.5	3.9	4.6	6.2 F
								11.2 Cl				11.3 Cl
1i	*p*-Cl	*m*-Cl	194	$C_{17}H_{13}Cl_2NO_2$	61.3	3.9	4.2	21.0	61.5	4.2	4.0	20.8
1j	*p*-Cl	*p*-F	198	$C_{17}H_{13}ClFNO_2$	64.3	4.1	4.4	6.0 F	64.4	4.3	4.7	6.3 F
								11.2 Cl				11.4 Cl
1k	*p*-Me	H	208	$C_{18}H_{17}NO_2$	77.4	6.1	5.0		77.2	6.2	5.3	
1l	*p*-Me	*o*-F	201	$C_{18}H_{16}FNO_2$	72.7	5.4	4.7	6.4	72.4	5.2	4.5	6.5
1m	*p*-Me	*m*-F	212	$C_{18}H_{16}FNO_2$	72.7	5.4	4.7	6.4	72.9	5.5	5.0	6.7
1n	*p*-Me	*m*-Cl	214	$C_{18}H_{16}ClNO_2$	68.9	5.1	4.5	11.3	68.7	5.3	4.7	11.5
1o	*p*-Me	*p*-F	205	$C_{18}H_{16}FNO_2$	72.7	5.4	4.7	6.4	72.8	5.5	4.4	6.6

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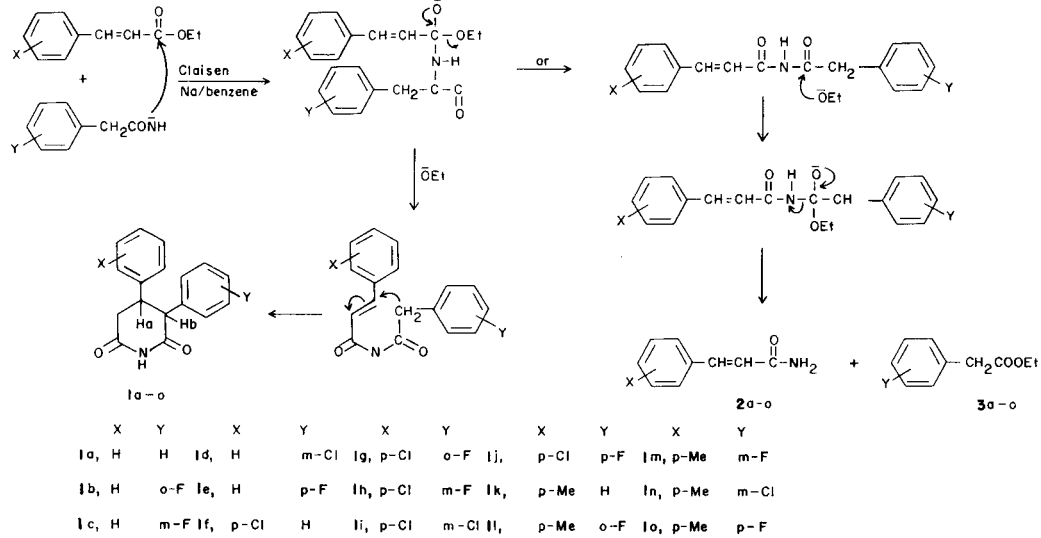
Table II

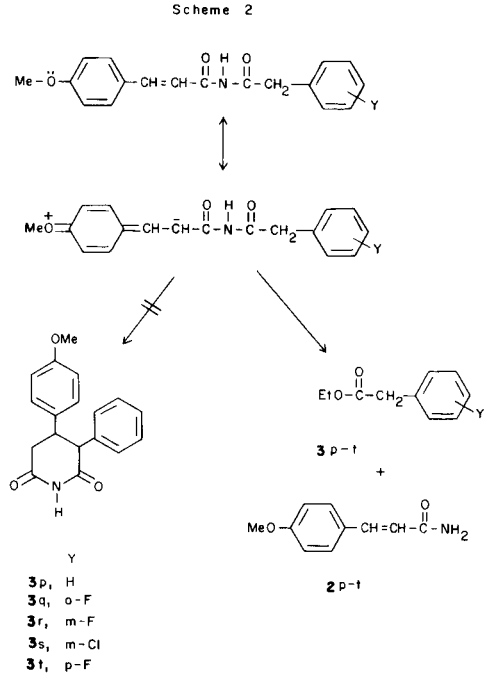
Substituted Cinnamides

Compound	X	M.p.°C	Formula	Analysis (%) Calcd. C	H	N	Halogen	Found C	H	N	Halogen
2f-g	*p*-Cl	204	C_9H_8ClNO	59.6	4.4	7.7	19.6	59.4	4.5	7.5	19.5
2k-o	*p*-Me	186	$C_{10}H_{11}NO$	74.5	6.8	8.7		74.3	7.0	8.8	
2p-t	*p*-MeO	190	$C_{10}H_{11}NO_2$	67.8	6.2	7.9		68.2	6.4	8.2	

Scheme 1



Scheme 2



from their spectral data. The ir spectral data of the imido compounds indicated the absence of the vinyl bond. It showed an absorption band near 3350 cm^{-1} which corresponded to the N-H stretching vibration and the bands at 1700 and 1720 cm^{-1} were characteristic of the carbonyl groups of the imido system (9). The nmr spectral data showed a doublet and a multiplet centered at δ 4.1 and 2.09 each integrating for one proton, characteristic of methine protons (H_b and H_a respectively), a doublet centered at δ 3.1 integrating for two protons for the methylene protons. The imido proton showed a resonance signal at around δ 8.4 and was exchanged by deuterium oxide.

The cinnamides isolated from the reaction products were identified on the basis of their elemental analysis, spectral data and their mixed melting points with an authentic sample.

EXPERIMENTAL

Unless otherwise stated, the ir spectra were measured in chloroform with a Unicam SP-200 instrument. ^1H Nmr spectra were determined with a Varian A-60D spectrometer for solutions in deuteriochloroform containing tetramethylsilane as the internal standard. Compounds were analyzed at the Max Planck Institute, Ruhr, West Germany. Melting points were determined on a Kofler hot stage and are uncorrected. Ethanol was used for crystallization.

Condensation of Ethyl Cinnamates and Arylacetamide. General Procedure.

Arylacetamide (0.0172 mole) was refluxed in dry benzene (150 ml.) with

powdered sodium (0.0172 g.-atom) for 24 hours. Ethyl cinnamate (0.0172 mole) was then added. The reaction mixture was kept under reflux for 24 hours. Then the reaction mixture was cooled and poured into 250 ml. of water. On cooling a solid was precipitated, identified as the corresponding cinnamide (**2a-t**). The organic layer (neutral fraction) was separated and washed with water. The alkaline aqueous layer was acidified with dilute sulphuric acid and was extracted with ether. The ethereal extracts were shaken with 10% sodium bicarbonate solution, which, on acidification, gave the acid fraction. The ethereal-benzene extracts (enol fraction) were dried and evaporated giving a solid (~1.5 g.). This was crystallized to give the corresponding 2,6-diketo-3,4-diarylpiperidine (**1a-o**); whereas if the *p*-methoxyethylcinnamate was used, a quantitative yield of *p*-methoxycinnamide was obtained.

Tlc for the neutral fraction showed the unreacted ethyl cinnamate as well as the produced arylacetate (**3a-t**) while the residual acid from the bicarbonate washing indicated a mixture of the corresponding arylacetic acid and cinnamic acid produced from the hydrolysis of the reactants and the products.

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