[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

Action of Grignard Reagents on Heterocyclic Compounds. II. Action of Grignard Reagents on Some Substituted Unsaturated Azlactones

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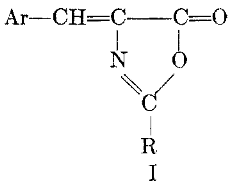
Various Grignard reagents were allowed to react with some substituted unsaturated azlactones (I) to give carbinols (II) and in some cases the corresponding oxazolines (III). The carbinols and the oxazolines were transformed to indene derivatives (IV) by the action of a hydrochloric acid–acetic acid mixture.

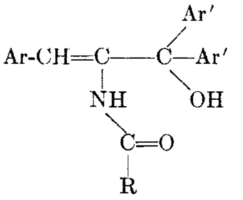
Recently, it has been shown[1,2,3,4] that 2-phenyl-4-benzylidene-5(4H)oxazolone (Ia) reacts with phenylmagnesium bromide to give mainly 1,1-diphenyl-2-benzamidocinnamyl alcohol (IIa); when this carbinol was treated with acetic anhydride and sodium acetate, 2,5,5-triphenyl-4-benzylidene-2-oxazoline (IIIa) was obtained. IIIa was also obtained from the Grignard reaction together with IIa when working under high concentrations. It was also shown[1] that when the carbinol (IIa) was treated with a hydrochloric acid–acetic acid mixture, boiling acetic or formic acid or boiling benzene in the presence of phosphorus pentoxide, 1,1-diphenyl-2-benzamido-indene (IVa) was formed.

This study is now extended to show the effect of substitution in the benzylidene radical, in the Grignard reagent used, or in the group attached in position 2 of the oxazolone ring, on the course of the reaction as it is assigned for each formula (*inter alia*). In all cases the carbinol (II) or the oxazoline (III) has been transformed to the corresponding indene derivative (IV) by the action of the hydrochloric acid–acetic acid mixture either cold or by mere warming.[1] The constitution of the products discussed here is based on the analogy with the products discussed in part I.[1]



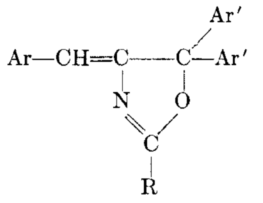
I

Ia. Ar = R = C_6H_5
Ib. Ar = p-$CH_3OC_6H_4$; R = C_6H_5
Ic. Ar = o-ClC_6H_4; R = C_6H_5
Id. Ar = C_6H_5; R = CH_3



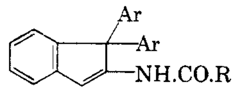
II

IIa. Ar = R = Ar′ = C_6H_5
IIb. Ar = R = C_6H_5; Ar′ = p-ClC_6H_4
IIc. Ar = R = C_6H_5; Ar′ = o-$CH_3OC_6H_4$
IId. Ar = p-$CH_3OC_6H_4$; R = Ar′ = C_6H_5
IIe. Ar = p-$CH_3OC_6H_4$; R = C_6H_5; Ar′ = p-ClC_6H_4
IIf. Ar = p-$CH_3OC_6H_4$; R = C_6H_5; Ar′ = o-$CH_3OC_6H_4$
IIg. Ar = o-ClC_6H_4; R = Ar′ = C_6H_5
IIh. Ar = o-ClC_6H_4; R = C_6H_5; Ar′ = p-ClC_6H_4
IIi. Ar = C_6H_5; R = CH_3; Ar′ = C_6H_5
IIj. Ar = C_6H_5; R = CH_3; Ar′ = p-ClC_6H_4
IIk. Ar = C_6H_5; R = CH_3; Ar′ = o-$CH_3OC_6H_4$



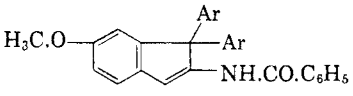
III

IIIa. Ar = R = Ar′ = C_6H_5
IIIb. Ar = R = C_6H_5; Ar′ = p-$CH_3OC_6H_4$
IIIc. Ar = p-$CH_3OC_6H_4$; R = C_6H_5; Ar′ = p-$CH_3OC_6H_4$
IIId. Ar = o-ClC_6H_4; R = C_6H_5; Ar′ = p-$CH_3OC_6H_4$
IIIe. Ar = C_6H_5; R = CH_3; Ar′ = p-ClC_6H_4
IIIf. Ar = C_6H_5; R = CH_3; Ar′ = o-$CH_3OC_6H_4$



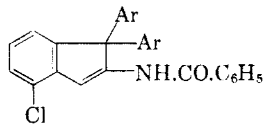
IV

IVa. Ar = C_6H_5; R = C_6H_5
IVb. Ar = p-ClC_6H_4; R = C_6H_5
IVc. Ar = o-$CH_3OC_6H_4$; R = C_6H_5
IVd. Ar = p-$CH_3OC_6H_4$; R = C_6H_5
IVe. Ar = C_6H_5; R = C_6H_5
IVf. Ar = p-ClC_6H_4; R = CH_3
IVg. Ar = o-$CH_3OC_6H_4$; R = CH_3



IV

IVh. Ar = C_6H_5
IVi. Ar = p-ClC_6H_4
IVj. Ar = p-$CH_3OC_6H_4$



IV

IVk. Ar = C_6H_5
IVl. Ar = p-ClC_6H_4
IVm. Ar = p-$CH_3OC_6H_4$

As far as the nature of the Grignard product is concerned, whether it is of type II or type III, Filler and Wismar[4] concluded from their experiments that the nature of the product depends upon

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[1] W. I. Awad and M. S. Hafez, *J. Org. Chem.*, in press.

[2] Mustafa and Harhash, *J. Org. Chem.*, 21, 575 (1956).

[3] Pourrat, *Bull. Soc. chim. France*, 828 (1955).

[4] Robert Filler and James D. Wismar, *J. Org. Chem.*, 22, 853 (1957).

TABLE I

COMPOUNDS OF STRUCTURE II

Compound	Solvent of Crystln.	M.P.°	Yield,[d] %	Formula[e]	Carbon, %		Hydrogen, %		Nitrogen, %		Color with Concd. H_2SO_4
					Calcd.	Found	Calcd.	Found	Calcd.	Found	
IIb		193	65	$C_{28}H_{21}NO_2Cl_2$[f]	70.88	70.61	4.43	4.68	2.95	2.82	Orange-red
IIc	c	180	68	$C_{30}H_{27}NO_4$	77.40	77.59	5.85	5.86	3.01	3.16	Violet
IId	c	149	72	$C_{29}H_{25}NO_3$					3.21	3.06	Orange
IIe	b	175	64	$C_{29}H_{23}NO_3Cl_2$	69.04	69.35	4.56	4.74	2.73	2.45	Orange
IIf	a	176	65	$C_{31}H_{29}NO_5$	75.13	75.26	5.90	5.96	2.83	2.99	Violet
IIg	a	142	67	$C_{28}H_{22}NO_2Cl$	76.39	76.35	5.01	5.07	3.19	3.34	Orange
IIh	a	172	65	$C_{28}H_{20}NO_2Cl_3$	66.10	66.66	3.93	3.99	2.75	2.39	Orange-yellow
IIj	b	178	68	$C_{23}H_{19}NO_2Cl_2$[g]	67.77	67.93	4.50	4.73	3.31	3.52	Orange-red
IIk	a	170	66	$C_{25}H_{25}NO_4$	74.44	73.80	6.20	6.06	3.47	3.34	Violet

[a] Benzene-petroleum ether (b.p. 40–60°). [b] Petroleum ether (b.p. 60–80°). [c] Benzene. [d] Yield is calculated as pure material. [e] All crystals were colorless. [f] Calcd.: Cl, 14.97. Found: Cl, 14.68. [g] Calcd.: Cl, 16.82. Found: Cl, 16.76.

TABLE II

COMPOUNDS OF STRUCTURE III

Compound	Method of Preparation	Solvent of Crystln.	M.P.°	Yield,[g] %	Formula[f]	Carbon, %		Hydrogen, %		Nitrogen, %		Color with Concd. H_2SO_4
						Calcd.	Found	Calcd.	Found	Calcd.	Found	
IIIb	a	c	183	68	$C_{30}H_{25}NO_3$	80.51	80.54	5.63	5.84	3.13	3.13	Orange-red
IIIc	a	d	146	71	$C_{31}H_{27}NO_4$	77.97	78.20	5.70	5.68	2.93	2.62	Red
IIId	a	d	173	65	$C_{30}H_{24}NO_3Cl$[h]	74.76	75.02	4.98	5.10	2.90	2.73	Red
IIIe	b	e	167	73	$C_{23}H_{17}NOCl_2$[i]	70.05	70.00	4.31	4.29	3.55	3.77	Orange-red
IIIf	b	c	161	66	$C_{25}H_{23}NO_3$	77.92	77.41	5.97	5.68	3.63	3.69	Very pale yellow

[a] *Via* Grignard reagent. [b] By the action of acetic anhydride and sodium acetate. [c] Petroleum ether (b.p. 60–80°). [d] Benzene-petroleum ether (b.p. 40–60°). [e] Methyl alcohol. [f] All crystals were colored yellow. [g] Yield is calculated as pure material. [h] Calcd.: Cl, 7.37. Found: Cl, 7.01. [i] Calcd.: Cl, 18.02. Found: Cl, 18.02.

TABLE III

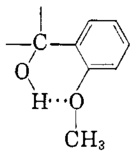
COMPOUNDS OF STRUCTURE IV

Compound	Solvent of Crystln.	M.P.°	Yield,[e] %	Formula[f]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Color with Concd. H_2SO_4
IVb	[b]	209	75	$C_{28}H_{19}NOCl_2$	73.68	73.95	4.17	4.30	3.07	3.03	15.57	15.36	Red
IVc	[b]	195	55	$C_{30}H_{25}NO_3$	80.51	79.87	5.63	5.75	3.13	3.51			Orange-red
IVd	[b]	199	78	$C_{30}H_{25}NO$	80.51	80.30	5.63	5.71	3.13	3.22			Light-brown
IVf	[b]	202	75	$C_{23}H_{17}NOCl_2$					3.55	3.59	18.02	17.38	Orange-red
IVg	[c]	134	59	$C_{25}H_{23}NO_3$	77.90	77.54	5.97	6.15	3.63	3.94			Olive-green
IVh	[d]	196	84	$C_{29}H_{23}NO_2$	83.45	83.93	5.55	5.69	3.35	3.04			Orange-yellow
IVi	[b]	195	77	$C_{29}H_{21}NO_2Cl_2$	71.60	71.72	4.32	4.66	2.88	2.77	14.60	14.02	Orange
IVj	[a]	188	73	$C_{31}H_{27}NO_4$	77.97	78.41	5.70	5.59	2.93	2.97			Red
IVk	[c]	165	81	$C_{28}H_{20}NOCl$	79.71	79.35	4.74	4.60	3.32	3.25	8.42	8.77	Orange
IVl	[a]	218	76	$C_{28}H_{18}NOCl_3$	68.52	69.38	3.66	3.97	2.85	2.69			Yellowish-green
IVm	[a]	189	79	$C_{30}H_{24}NO_3Cl$	74.76	75.02	4.98	4.99	2.90	2.74	7.37	7.11	Orange-red

[a] Benzene-petroleum ether (b.p. 40–60°). [b] Petroleum ether (b.p 60-80°). [c] Methyl alcohol. [d] Benzene. [e] Yield is calculated as pure material. [f] All crystals were colorless.

the total volume of solvent used in the Grignard reaction. However, we believe that the nature of the Grignard reagent itself has a more pronounced effect on the nature of the Grignard product. When phenylmagnesium bromide, *p*-chlorophenylmagnesium bromide, or *o*-anisylmagnesium bromide are allowed to react with Ia, Ib, Ic, and Id, compounds of type II are the predominant products. When *p*-anisylmagnesium bromide is used, the main product is of type III and no carbinol has been isolated even using lower concentrations. This can be attributed to the high + T effect of the *p*-anisyl group, which facilitates the liberation of the hydroxylic group of the carbinol as a hydroxide ion.

The fact that in the case of the *o*-anisyl derivative the carbinol II and not the oxazoline (III) is obtained is not incompatible, as the possible chelation of the *o*-methoxyl group with the hydrogen of the hydroxylic group definitely reduces its plus T effect in comparison with the case of the *p*-anisyl group (cf. V).



V

EXPERIMENTAL[5]

General procedure for the reaction of oxazolone (I) *with arylmagnesium halides.* To an ethereal solution of the arylmagnesium halide (3 moles) was added a fine suspension of the oxazolone (I) (1 mole) in ether. The reaction mixture was refluxed for 2 hr. and left overnight. It was hydrolyzed with a saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath nearly to dryness. The oily residue thus obtained was triturated with petroleum ether (b.p. 40–60°) or with methyl alcohol and allowed to cool. The product was filtered and crystallized from a suitable solvent, (*cf.* Tables I and II).

Action of a hydrochloric acid–acetic acid mixture on the carbinol II *or the oxazoline* III. To a fine suspension of II or III (1.0 g.) in acetic acid (20 ml.), hydrochloric acid (10 ml.) (sp. gr. 1.18) was added. The substance went gradually into solution (yellow-brown color). The reaction mixture was warmed on a water bath and left at room temperature for 30 min. A colorless product (IV) separated; it was filtered, washed with water, and crystallized from a suitable solvent (*cf.* Table III).

Action of acetic anhydride and sodium acetate on the carbinol II. II (1.0 g.) was refluxed with acetic anhydride (50 ml.) and fused sodium acetate (0.5 g.) for 3 hr. The reaction mixture was poured on ice while hot and left overnight. The yellow substance thus obtained was filtered, washed with water, and crystallized from a suitable solvent (*cf.* Table II).

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(5) Microanalyses were carried out by Alfred Bernhardt, im Max-Planck Institut, Mülheim (Rühr) Germany. The melting points are not corrected.