A GENERAL MECHANISM FOR REACTIONS OF 4-OXO-3*H*-QUINAZOLINES WITH GRIGNARD REAGENTS*

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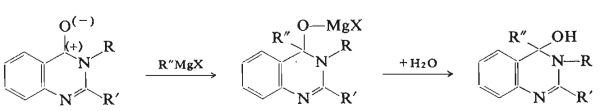
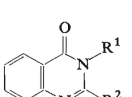
Reactions of Grignard reagents with 4-oxo-3*H*-quinazolines *Ia—If*, both in normal and inverse additions, were studied. A general reaction mechanism to account for the varied reaction products is postulated.

It has been shown that 3-phenyl-4-oxo-3*H*-quinazoline with benzylmagnesium chloride afforded diphenylisopropylanthranilide[1], 2-substituted 4-oxo-3*H*-quinazolines with Grignard reagents undergo 1,2-addition on the carbonyl group to give the corresponding carbinols[2,3], while 2,3-diphenyl-4-oxo-3*H*-quinazoline with phenylmagnesium bromide gave 2,4,4-triphenylbenzoxazine and aniline[3]. It has also been shown that different products were obtained from normal and inverse additions of the same reagents. The diverse behaviour of these compounds led us to study more fully reactions of 4-oxo-3*H*-quinazolines *Ia—If*.

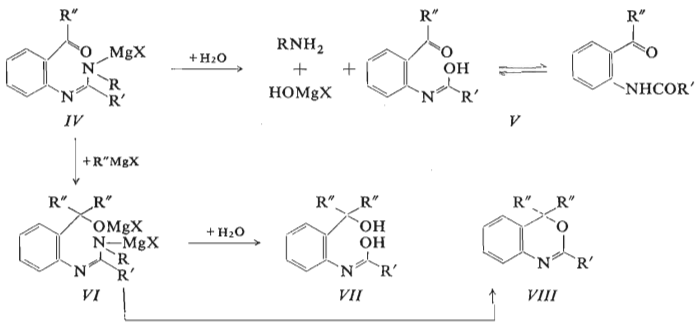


I *II* *III*



Ia, $R^1 = R^2 = C_6H_5$
Ib, $R^1 = C_6H_4OCH_3$-(4), $R^2 = C_6H_5$
Ic, $R^1 = CH_3$, $R^2 = C_6H_5$
Id, $R^1 = C_6H_5$, $R^2 = CH_3$
Ie, $R^1 = C_6H_4OCH_3$-(4), $R^2 = CH_3$
If, $R^1 = C_2H_5$, $R^2 = CH_3$

* Part V in the series Heterocyclic Nitrogen Compounds; Papers Abdel-Megied F. M. E., Elkaschef M. A.-F., Mokhtar K.-E. M., Zaki K.-E. M. J. Chem. Soc. C *1971*, 1055, and Abdel-Megeid F. M. E., Elkaschef M. A.-F. Kokhtar, K.-E. M., Yassin S. M. A.: J. Prakt. Chem. *313*, 1143 (1971) are to be considered as parts III and IV of this series.



	R	R′	R″		R″		R′	R″
IIIa,	C_6H_5	C_6H_5	C_6H_5	*Va*,	C_6H_5	*VIIIa*,	C_6H_5	C_6H_5
IIIb,	C_6H_5	CH_3	$C_{10}H_7(\alpha-)$	*Vb*,	C_6H_5	*VIIIb*,	CH_3	C_6H_5
IIIc,	C_6H_5	C_6H_5	C_2H_5	*Vc*,	CH_3	*VIIIc*,	C_6H_5	$C_{10}H_7(\alpha-)$
IIId,	$C_6H_4OCH_3$-(4)	C_6H_5	C_2H_5	*Vd*,	CH_3	*VIIId*,	CH_3	C_2H_5

SCHEME 1

We found that phenylmagnesium bromide with 2,3-diphenyl-4-oxo-3*H*-quinazoline (*Ia*) gave 4-hydroxy-2,3,4-triphenyl-3*H*-quinazoline (*IIIa*) along with 2,4,4-triphenyl-3,1-benzoxazine (*VIIIa*). α-Naphthylmagnesium bromide with 2-methyl-3-phenyl-4-oxo-3*H*-quinazoline (*Id*) gave 4-hydroxy-4-α-naphthyl-2-methyl-3-phenyl-3*H*-quinazoline (*IIIb*). Ethylmagnesium bromide with 2,3-diphenyl-4-oxo-3*H*-quinazoline (*Ia*) and with 2-phenyl-3-(4-methoxyphenyl)-4-oxo-3*H*-quinazoline (*Ib*), however, gave 2,3-diphenyl-4-hydroxy-4-ethyl- (*IIIc*) and 2-phenyl-3-(4-methoxyphenyl)-4-hydroxy-4-ethyl-3*H*-quinazoline (*IIId*). This reaction leading to the formation of 4-hydroxy-3*H*-quinazolines (*III*) ought to have taken place by a 1,2 addition to the carbonyl group as shown in formula *II*.

Phenylmagnesium bromide with *Ia*–*Id* gave substituted 4,4-diphenyl-3,1-benzoxazines *VIIIa* and *VIIIb*. Similarly, α-naphthylmagnesium bromide gave 4,4-di-α-naphthyl-2-phenyl-3,1-benzoxazine (*VIIIc*) with compounds *Ia*–*Ic*. With ethylmagnesium bromide 2-methyl-3-phenyl-4-oxo-3*H*-quinazoline (*Id*) gave 4,4-diethyl-2-methyl-3,1-benzoxazine (*VIIId*).

A general mechanism leading to compounds mentioned above could be postulated (Scheme 1). The first step is a nucleophilic attack on the carbonyl group to give *II* which on hydrolysis affords *III*. Compound *II* may undergo ring cleavage to give *IV* which reacts with another molecule of Grignard reagent to give *VI* or hydrolysed to give *V*. Compound *VI* may give *VIII* directly or *via VII*. Compound *III*, *V* and *VIII* were actually isolated; infrared spectra are given in Tables I–III. Also, in favour

of this reaction mechanism is the separation of the products of more than one step together, *e.g.* isolation of 4-hydroxy-1,2,4-triphenyl-3*H*-quinazoline (*IIIa*) along with 2,4,4-triphenyl-3,1-benzoxazine (*VIIIa*) from the same reaction mixture and also *Vd* and *VIIId* together, from another reaction mixture.

A further proof of this reaction mechanism was sought in the inverse addition. Mustafa and coworkers[4] using excess of the Grignard reagent stated that the same products were obtained from the normal and inverse addition. As the reaction depends on the ratio between the Grignard reagent and the quinazoline in the reaction mixture, we used only one molecule of the Grignard reagent to one of the quinazolone. So, it was possible to isolate the amino ketones *Va* and *Vb* from the reaction of compound *Ia* with phenyl- and α-naphthylmagnesium bromide, respectively, and *Vc* ans *Vd* from the reaction of *Id* with phenyl- and ethylmagnesium bromide, respectively. Phenylmagnesium bromide with *Ic* afforded N-benzoylanthranilic acid N'-methylamide as a result of hydrolysis of *Ic*. The other compounds gave back the starting quinazolones.

Compounds *Ie* and *If*, on normal addition, gave no reaction. In case of *If*, the inductive effect of the ethyl group in $N_{(3)}$ and the methyl group in $C_{(2)}$ forming a longer chain linked to $N_{(3)}$ partially eliminates the positive charge on $C_{(4)}$, while in compound *Ie* the compensation is accomplished by the tautomeric effect of *para*-methoxyl group. As a result, the nucleophilic attack is inhibit. The tautomeric effect of the *para*-methoxyl group alone was not sufficient to inhibited the nucleophilic attack, since 2-phenyl-3-(4-methoxyphenyl)-4-oxo-3*H*-quinazoline (*Ib*) reacted readily with Grignard reagents. This effect was shown prominently in case of the inverse addition where the presence of an alkyl group adjacent to the carbonyl group (on $N_{(3)}$) inhibited its reaction, while a methyl group at $C_{(2)}$ did not interfere. So, one can deduce that tautomeric effect or inductive effect alone is not sufficient to inhibit the reaction completely.

TABLE I

Selected Bands (wavenumbers in cm^{-1}) in IR Spectra of 4-Hydroxy-2,3,4-trisubstituted 3*H*-Quinazolines *III*

Compound	Solvent	ν(OH)	ν(C—O)	ν(C=N)	tert N
IIIa	nujol	3 200—3 400	1 140	1 625	1 360
IIIb	KBr	3 200—3 600	1 140	1 625	1 360
IIIc	nujol	3 200—3 600	1 140	1 625	1 360
IIId	nujol	3 200—3 400	1 140	1 625	1 360

EXPERIMENTAL

Melting points are uncorrected. Analyses are done by the Microanalytical Laboratory, N.R.C., Cairo.

2,3-Diphenyl-4-oxo-3*H*-quinazoline (*Ia*)

A mixture of 2-phenyl-3,1-benzoxaz-4-one (5 g, 0·02 mol) and aniline (5 g, 0·053 mol) was refluxed for 4 h. The excess of aniline was evaporated. The residue was kept for 4 h at 240—250°C, crystallised from a mixture of n-hexane–ethyl acetate and recrystallised therefrom to give crystals (5 g, 97%) m.p. and mixed m.p. (with compound prepared according to[4]) 157°C.

2-Phenyl-3-(4-methoxyphenyl)-4-oxo-3*H*-quinazoline (*Ib*)

In a reaction as above, using 2-phenyl-3,1-benzoxaz-4-one (0·02 mol) and *p*-anisidine (3·69 g, 0·03 mol) the resulting mass crystallised from n-hexane–ethyl acetate gave *Ib* (5 g, 72%); m.p. 206°C. For $C_{21}H_{16}N_2O_2$ (328) calculated: 76·83% C, 4·88% H, 8·54% N; found: 76·52% C, 4·65% H, 8·37% N.

TABLE II

Selected Bands (wavenumbers in cm^{-1}) in IR Spectra of Amido Ketones *V*

Compound	Solvent	Amide-I band	Amide-II band	ν(NH)	Phenyl	Alkyl
Va	nujol	1 660	1 550—1 530	3 200	1 600	—
Vb	KBr	1 680	1 550—1 530	3 200—3 300	1 600	—
Vc	KBr	1 680	1 560	3 080—3 020	1 600	3 000—2 800
Vd	nujol	1 660	1 560	3 280—3 100	1 600	3 000—2 800

TABLE III

IR Spectra of 4,4-Disubstituted 3,1-Benzoxazines *VIII* (cm^{-1})

Compound	Solvent	ν(C—O—C) cyclic	Aromat.	ν(C=N)	Alkyl
VIIIa	nujol	1 250	1 600	1 625	—
VIIIb	KBr	1 225	1 600	1 625	—
VIIIc	nujol	1 225	1 600	1 625	—
VIIId	KBr	1 225	1 600	1 600	2 800—3000

TABLE IV

Products from the Reaction of Grignard Reagents (R″MgX) with 4-Oxoquinazolines

Starting compound (R″)	Product (solvent)[a]	M.p. °C (yield, %)	Formula (m. w.)	Calculated/Found % C	% H	% N
			Normal addition			
Ia	*IIIa*	290	$C_{22}H_{20}N_2O$	80·49	6·10	8·54
(C_2H_5)	(A)	(30·4)	(328)	80·82	5·95	8·06
Ia	*VIIIa*	218	$C_{26}H_{19}NO$	86·42	5·26	3·87
(C_6H_5)	(B)	(27·7)	(361)	85·89	5·41	4·04
Ia	*IIIa*	230	$C_{26}H_{20}N_2O_2 \cdot {}^1/_2 C_2H_5OH$	81·20	5·76	7·02
(C_6H_5)	(C)	(5·3)	(399)	81·47	5·46	6·92
Ia	*VIIIc*	238	$C_{34}H_{23}NO$	88·50	4·99	3·03
(α-naphthyl)	(C)	(43·4)	(461)	88·49	5·13	3·03
Ib	*IIId*	168	$C_{23}H_{22}N_2O_2$	77·09	6·14	7·82
(C_2H_5)	(B)	(55·8)	(358)	76·91	6·50	8·13
Ib	*VIIIa*	218	—	—	—	—
(C_6H_5)	(D)	(66·0)				
Ib	*VIIIc*	238	—	—	—	—
(α-naphthyl)	(C)	(47·5)				
Ic	*VIIIa*	218	—	—	—	—
(C_6H_5)	(D)	(52·6)				
Ic	*VIIIc*	238	—	—	—	—
(α-naphthyl)	(C)	(54·0)				
Id	*VIIId*	180	$C_{13}H_{17}NO$	76·35	8·37	6·79
(C_2H_5)	(E)	(49·2)	(203)	76·51	7·92	7·12
Id	*Vd*	276	$C_{11}H_{13}NO_2$	69·10	6·81	7·33
(C_2H_5)	(F)	(8·0)	(191)	69·22	6·35	6·98
Id	*VIIId*	220	$C_{21}H_{17}NO$	84·28	5·78	4·68
(C_6H_5)	(E)	(33·3)	(299)	83·93	5·84	5·10
Id	*IIIb*	220	$C_{25}H_{20}N_2O$	82·42	5·48	7·69
(α-naphthyl)	(B)	(43·7)	(364)	81·80	5·30	8·10
			Inverse addition			
Ia	*Va*	285	$C_{20}H_{17}NO_3$	75·24	5·33	4·39
(C_6H_5)	(G)	(12·5)	(319)	74·72	5·30	3·95
Ia	*Vb*	290	$C_{24}H_{17}NO_2$	82·05	4·83	4·37
(α-naphthyl)	(G)	(21·0)	(351)	81·71	4·47	3·99
Id	*Vd*	267	—	—	—	—
(C_2H_5)	(F)	(20·0)				
Id	*Vc*	168	$C_{15}H_{13}NO_2$	75·31	5·44	5·86
(C_6H_5)	(B)	(16·3)	(239)	75·24	5·69	5·81

[a] A Benzene–methanol, B benzene–ligroine (b.p. 70—80°C), C benzene–ethanol, D benzene, E benzene–n-hexane, F ethanol, G aqueous dioxane.

2-Methyl-3-(4-methoxyphenyl)-4-oxo-3*H*-quinazoline (*Ie*)

From a reaction as above using *p*-anisidine (4·6 g, 0·037 mol) and 2-methyl-3,1-benzoxazone (6·0 g, 0·037 mol) a solid mass (6·0 g, 67%) was obtained, that crystallised from n-hexane–ethyl acetate and melted at 168°C. For $C_{16}H_{14}N_2O_2$ (266) calculated: 72·18% C, 5·26% H, 10.52% N; found: 72·62% C, 5·41% H, 9·82% N.

Action of Grignard Reagent on 4-Oxo-3*H*-quinazolines

A) *Normal addition*: A cold solution of the quinazoline (0·01 mol) in benzene (50 ml) was added to a cold solution of the Grignard reagent (0·05 mol) in ether (50 ml). The mixture was left overnight, refluxed for 4 h and cooled. It was then decomposed with cold ammonium chloride solution, extracted with ether and the ethereal solution was dried (Na_2SO_4), filtered, and evaporated. The residue was crystallised from the proper solvent. In some experiments, on evaporation of the mother liquor of crystallisation, another product, which was crystallised from the proper solvent, was obtained (Table IV).

B) *Inverse addition*: To a cold solution of the 3*H*-quinazoline (0·01 mol) in benzene (50 ml), was added a cold solution of the Grignard reagent (0·01 mol) in ether (50 ml). The reaction mixture was worked out as in the preceding experiment Table IV).

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