Pak. j. sci. ind. res., vol. 34, nos. 7-8, July-August 1991

SYNTHESIS AND REACTIONS OF 4-ARYLIDENE/OR (HALOPHTHALYLIDENE)-2-ARYL-Δ^2-OXAZOLINE-5-ONE WITH SOME NUCLEOPHILES

M. A. EL-HASHAH, HASSAN M. F. MADKOUR AND M. S. AMINE*
Chemistry Department, Ain Shams University, Abbassia, Cairo, Egypt

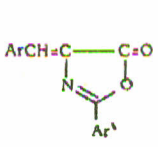
(Received July 28, 1990; revised September 4, 1991)

The behavior of oxazolone derivatives (I) and (II) toward some nitrogen, oxygen and carbon nucleophiles has been described.

Key words: 4-Arylidene oxazolone, Halophthalylidene oxazolone and Heterocyclic introgen compounds.

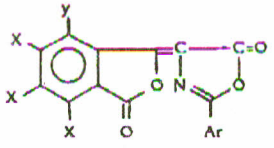
Introduction

2-Aryl-4-arylidene-5(4)-oxazolones (1a-c) and 2-aryl-4-phthalylidene 5(4)-oxazolones (IIa-d) have been synthesised via condensation of aromatic aldehydes [namely, *p*-chlorobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, 3-naphthaldehyde and tetrachloro-, tetrabromo-, and 3-nitrophthalic anhydride] with aroyl glycine, via Erlenmeyer synthesis [1].



(I)

Ar	Ar¹
a, C_6H_4. Cl (p)	C_6H_4 .Cl(o)
b, $C_6H_2(OCH_3)_3$ (3,4,5)	C_6H_4 .Cl(o)
c, $C_{10}H_7$ (β)	C_6H_5



(II)

X	Y	Ar
a, Cl	Cl	C_6H_5
b, Cl	Cl	C_6H_4.Cl(o)
c, Br	Br	C_6H_5
d, H	NO_2	C_6H_4.Cl(p)

Compounds (I) exhibit strong absorption band in the IR in the region (1750-1760)+ corresponding to υC=O of azlactone nucleus.

It was reported that [2] phthalic anhydride reacted with 2-furoylglycine and gave 4-phthalylidene-2-(2'-furyl)-5-(4)-oxazolone. In this investigation we sought to augment the reactivity of phthalic anhydride towards condensation with aroylglycine by introducing electron attracting groups (e.g. chloro or bromo) in the aromatic moiety, in an attempt to improve the yield of the products and contrasting the reactivity of furanone and oxazolone nuclei toward nucleophiles.

Thus tetrachloro and/or tetrabromophthalic anhydride derivatives were condensed with aroylglycine derivatives in the presence of a mixture of sodium acetate and acetic anhydride to give 4-(3', 4',5',6'-tetrachloro and/or tetrabromophthalylidene-2-aryl-5(4)-oxazolones (IIa-c). The IR spectra of the compounds (II) exhibited strong absorption in the region 1790-1800 ($\upsilon_{C=O}$) of υ-lactone), 1730-1740 ($\upsilon_{C=O}$ of oxazolone), and 1460-1650 ($\upsilon_{C=N}$).

In continuation of our work reported ealier on the behaviour of 2-aryl-4-arylidene-5(4)-oxazolones toward nitrogen nucleophiles and aromatic hydrocarbon [3,4], the present investigation describes the reaction of (Ia) with amino acids. Thus compound (Ia) reacts with 3-aminopropionic acid, DL-lucine, and phenylalanine in boiling aqueous pyridine to give o-(o-chlorobenzolyamino)-β-(*p*-chlorophenyl)-N-(alkyl/or aralkyl) acrylamide (IIIa-c).

IR spectra of compounds (III_{a-c}) showed bands in the region (1700-1710) attributable to $\upsilon_{C=O}$ of carboxylic group, in the region (1650-1670) due to $\upsilon_{C=O}$ of carboxamide, 3200 (υ_{NH}) and 3350 (broad) due to υ_{OH}.

On the other hand, when compound Ia was allowed to react with anthranilic acid in refluxing *n*-butanol afforded 2-[α-*o*-chlorobenzoylamino β-*p*-chlorophenyl) vinyl]-4H-3, 1-benzoxazine-4-one (IV_a) IR spectrum of compound IV_a exhi-bits absorption bands at 1750 ($\upsilon_{C=O}$ of oxazinone nucleus), 1665 ($\upsilon_{C=O}$ of carboxamide) and 3350 (υ_{NH}) which agree well with the proposed structure.

Compound Ib reacts with methylanthranilate in boiling *n*-butanol to give IV_b.

IR spectrum of compound IV_b exhibits absorption bands at 1755, 1665, and 3250 attributable to $\upsilon_{C=O}$ of oxazinone nucleus, carboxamide and $_{NH}$ respectively.

The reaction of Ia with *p*-toluidine in refluxing ethanol gave α-(*o*-chlorobenzoylamino)-β-(*p*-chlorophenyl-N-*p*-tolylacrylamide IIId.

The IR opectrum of IIId showed bands at 1660, 1670 (υ_{CO} of amide) and 3170, 3200 (υ_{NH}).

On the other hand, compound (Ic) when submitted to react with *m*-toluidine in refluxing acetic acid in presence of anhydrous sodium acetate the imidazolone V was obtained.

In the present work the authors investigated the reaction of (Ib) with ethylacetoacetate in refluxing *tert.* but anol in presence of potassium *tert.* butoxide as a catalyst, the diketone (IIIe) was obtained. Thus, it is envisaged that the formation of (IIIe) involves the opening of heterocyclic ring of (Ib), with the carbanion of active methylene

* Benha University, Faculty of Science, Benha, Egypt.

+υ_{max} in cm^{-1} throughout the paper.

group followed by ketonic hydrolysis and decarboxylation of unstable β-keto acid.

IR spectrum of IIIe which exhibited υ_{max} at 1710, 1690 (υ_{CO} of two carbonyl groups), 1660 (υ_{CO} carboxamide) and υ_{NH} 3200.

Compound (Ic) undergoes hetero ring opening with sodium ethoxide in boiling ethanol to give the ester (IIIf). The constitution of this ester was inferred from, its IR spectrum which reveals bands at 1745 (υ_{CO} of ester), 1660 ($\upsilon_{C=O}$ of carboxamide) and 330 (υ_{NH}).

The reaction of IIa with *m*-chloroanaline in molar ratio (1:1) in refluxing ethanol gave the corresponding phthalylidene-N-(3-chlorophenyl) hippeuric acid amide derivative (VIa). Its IR spectrum exhibits bands at 1770 ($\upsilon_{C=O}$ of γ-lactone) 1670, 1655 ($\upsilon_{C=O}$ of carboxamide) and 3200 (υ_{NH}).

Treatment of compound (IIa) with alcoholic sodium hydroxide yielded the phthalylidene hippuric acid (VIb), its IR spectrum shows absorption bands at 1770, 1690, 1660 and 3170 attributable to υ_{max} of three carbonyl groups and υ_{NH} respectively.

The oxazolone derivatives (IIb and c) on fusion with benzylamine in oil bath at 170° gave the corresponding imidazolones (VIIa and b) respectively, while the oxazolone IIc reacted with analine in molar ratio (1:1) in refluxing toluene giving the imidazolone (VIIc). From a formentioned results we concluded that, the oxazolone nucleus is highly reactive than the furanone nucleus towards nitrogen nucleophiles, which may be ascribed to steric and polar factors in the substrates (vide infra).

Reactions of IId (1 mole) with cyclohexylamine (1 mole) in refluxing toluene yielded 4-(3-nitrophthalylidene)-1-cyclohexyl-2-(4-chloro phenyl)-5-imidazolone (VIId).

The strong polarisation of carbonyl group caused by chlorine atom of *p*-chlorophenyl and the large nucleophilicity of nitrogen of cyclohexylamine moiety reinforce each other and augment the rate of cyclisation under these experimental conditions. The IR spectrum of VIId showed υ_{max} of two carbonyl groups at 1725 and 1690 and $\upsilon_{C=N}$ at 1620 which agree well with the proposed structure.

On the other hand the reaction of IId (1 mole) with cyclohexylamine (2 mole) in refluxing toluene afforded a mixture of the imidazolone (VIId) and 4-[(6-nitro-2-phenyl carbamoyl) benzoyl]-1-cyclohexyl-2-(4-chlorophenyl)-5-imidazolone (VIII). Its IR spectrum showed characteristic absorption bands at 1690, 1680, 1640 attributable to three carbonyl groups and other two additional bands at 1620 and 3260 due to $\upsilon_{C=N}$ and NH respectively.

From the above results, the authors conclude that the azlactone is more easily opened by amines than the lactone ring. In order to explain the relative reactivity of azlactone ring compared with the lactone ring, we have to take into consideration both the polar and steric factors:

(i). The polar effect of the nitro group activates the carbonyl group of the azalactone towards nitrogen nucleophiles.

(ii). The approach of the bulky cyclohexyl group to the reacton site of the lactone ring was sterically hindered and hence required high energy.

This explains why the lactone ring is not opened on using one mole of the cyclohexylamine.

Reaction of IId with excess N_2H_4 in refluxing ethanol gave amixture of 5-nitrophthalazin-1, 4-dione (IX) and *p*-chlorobenzoylglycine hydrazide (X),

The structure of phthalazindione was established by its unambiguous synthesis involving reaction of 3-nitrophthalic anhydride with hydrazine hydrate in refluxing ethanol and comparison of the m.p. and mixed m.p.

On the other hand, the condensation of (IId) with excess phenylhydrazine in boiling alcohol yielded a mixture of 3-nitrophlic acid *bis*-phenylhydrazide (XI) and *p*-chlorobenzoylglycine-*N*-phenylhydrazide (XII).

The structure (XI) was established from comparison with authentic sample prepared from the reaction of 2-nitrophthalic anhydride (1 mole) and phenylhydrazine (4 moles) in refluxing ethanol for 6 hrs. The IR spectrum of compound (XII) displayed strong absorption bands at 1670, 1660, and 3340 attributable to $\upsilon_{C=O}$ groups and υ_{NH}.

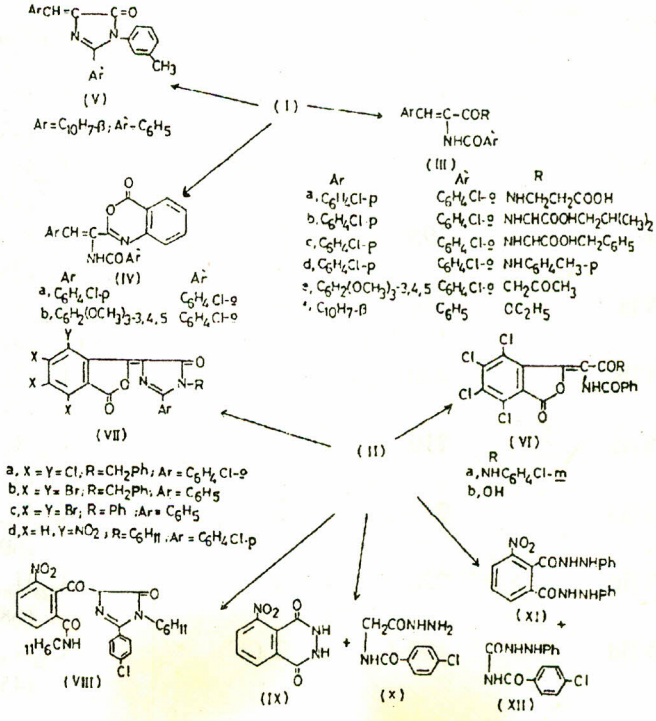


TABLE 1. PHYSICAL DATA AND CHARACTERIZATION OF SYNTHESISED COMPOUNDS.

Compound	M.P. (°C)	Crystallization solvent (yield%)	Formula (M. Wt.)	Analysis % (Calcd.)/Found		
				C	H	N
Ia	215	T (60)	$C_{16}H_9Cl_2NO_2$	(60.38)	(2.83)	(4.40)
			(318)	60.22	2.30	4.61
Ib	169	A (59)	$C_{19}H_{16}ClNO_5$	(61.04)	(4.28)	(3.75)
			(373.5)	61.18	4.16	3.90
Ic	162	L.P./100-120°	$C_{20}H_{13}NO_2$	(80.27)	(4.35)	(4.68)
		(60)	(249)	80.32	4.52	4.99
IIa	over 280	T (62)	$C_{17}H_5Cl_4NO_4$	Cl	(33.10)	–
			(429)	–	32.85	–
IIb	over 300	T (63)	$C_{17}H_4Cl_5NO_4$	Cl	(38.30)	–
			(463.5)	–	38.16	–
IIc	over 270	A (62)	$C_{17}H_5Br_4NO_4$	Br	(52.69)	–
			(606.6)	–	52.22	–
IId	216	B (41)	$C_{17}H_7ClN_2O_6$	(55.00)	(1.89)	(7.56)
			(370.5)	55.36	1.62	7.21
IIIa	175	dil. M (62)	$C_{19}H_{16}Cl_2N_2O_2$	(56.02)	(3.93)	(6.88)
			(407)	56.63	3.71	7.12
IIIb	170	M (55)	$C_{22}H_{22}Cl_2N_2O_4$	(58.80)	(4.90)	(6.24)
			(449)	58.61	4.82	6.80
IIIc	182	dil. M	$C_{25}H_{20}Cl_2N_2O_4$	(62.11)	(4.14)	(5.80)
			(483)	61.88	4.50	6.12
IIId	195	B (65)	$C_{23}H_{18}Cl_2N_2O_2$	(64.94)	(4.24)	(6.59)
			(425)	65.12	4.67	7.15
IIIe	230	A (42)	$C_{22}H_{22}ClNO_6$	(61.18)	(5.10)	(3.24)
			(431.5)	61.77	4.89	3.70
IIIf	157	B (52)	$C_{22}H_{19}NO_3$	(76.52)	(5.51)	(4.06)
			(345)	76.69	5.11	4.13
IVa	170	B (62)	$C_{23}H_{14}Cl_2N_2O_3$	(63.16)	(3.20)	(6.41)
			(437)	62.85	3.45	6.70
IVb	170	A (65)	$C_{26}H_{21}ClN_2O_6$	(63.35)	(4.26)	(5.69)
			(492.5)	63.82	4.71	6.15
V	195	E	$C_{27}H_{20}N_2O$	(83.51)	(5.15)	(7.22)
			(388)	82.99	5.62	7.32
VIa	259	B	$C_{23}H_{11}Cl_5N_2O_4$	Cl	(31.90)	N (5.03)
			(556.5)	–	32.37	5.31
VIb	230	A	$C_{17}H_7Cl_4NO_5$	Cl	(31.77)	N (3.13)
			(447)	–	31.29	3.46
VIIa	210	A	$C_{24}H_{11}Cl_5N_2O_3$	Cl	(32.31)	N (5.07)
			(552.5)	–	32.55	5.73
VIIb	249	B	$C_{24}H_{12}Br_4N_2O_3$	Br	(45.95)	N (4.03)
			(695.6)	–	45.48	4.31
VIIc	220	T	$C_{23}H_{10}Br_4N_2O_3$	Br	(46.89)	N (4.10)
			(681.6)	–	46.45	3.99
VIId	190-1	T (70)	$C_{23}H_{18}N_3O_5Cl$	(61.13)	(3.98)	(9.30)
			(451.5)	61.25	3.71	9.01

(Continue...)

(Table 1 Contd... . ..)

VIII	175-76	L.P. (60-80°) (35)	$C_{29}H_{31}N_4O_5Cl$ (550.5)	(63.21) 63.01	(5.63) 5.81	(10.17) 10.53
IX	280	B (50)	$C_8H_5N_3O_4$ (207)	(46.38) 46.11	(2.42) 2.29	(20.29) 19.99
X	160-1	M.P.(60-80°) (25)	$C_9H_{10}N_3O_2Cl$ (227.5)	(47.47) 47.32	(4.39) 4.51	(18.46) 18.46
XI	290	B (61)	$C_{20}H_{17}N_5O_4$ (391)	(61.38) 61.16	(4.35) 4.19	(17.90) 17.18
XII	122-3	L.P.(60-80°) (20)	$C_{15}H_{14}N_3O_2Cl$ (303.5)	(58.30) 58.21	(4.60) 4.12	(13.87) 13.35

B=Benzene, L.P.=Light petrol, T=Toluene, E=Ethanol, A=Acetic acid, M=Methanol.

Experimental

Melting points reported are uncorrected. The IR (KBr) spectra are measured on a Unicam SP 1200 spectrophotometer. Characterisation and physical data are given in Table 1.

Synthesis of compounds (Ia-c) and (IIa-d). A mixture of the aromatic aldehyde, (p-chlorobenzaldehyde, 3,4,5-trimethoxy benzaldehyde, β-naphthaldehyde (0.12 mole) with aroylglycine (0.01 mole), and a mixture of appropriate phthalic anhydride (0.12 mole) with aroylglycine (0.1 mole) in acetic anhydride (20 mole) and fused sodium acetate (0.5gm) when heated on a water both for 3 hrs and then cooled gave (Ia-c) and (IIa-d) respectively. The solid products were crystalized from proper solvents.

Synthesis of (IIIa-c). A solution of Ia (0.01 mole) and the appropriate amino acid (β-aminopropionic acid, DL-lucine, phenylalaine) (0.01 mole) in aqueous pyridine (40 ml) was heated under reflux for 3 hrs then poured into ice-HCl. The solid products were filtered off and recrystallised from suitable solvents to give IIIa-c.

Formation of IVa and/or IIId. A solution of Ia (0.01 mole) and anthranilic acid or *p*-toluidine (0.01 mole) in *n*-butanol or ethanol (40 ml) was heated under reflux for 6 hrs. The product IVa or IIId that deposited on cooling was crystallised from suitable solvents.

Formation of IVb. A mixture of Ib (0.01 mole) and methyl anthranilate (0.01 mole) in *n*-butanol was refluxed for 4 hrs and cooled. The solid that separated was collected and recrystallised from the proper solvent to give IVb.

Reaction of (Ib) with ethyl acetoacetate: Formation of the diketone IIIe. A solution of (Ib) (0.01 mole), ethyl acetoacetate (0.015 mole) and potassium *tert*-butoxide (0.011 mole) in *tert*-butyl alcohol (30 ml) was heated under reflux for 8 hrs. The reaction mixture was cooled and poured into ice/dil hydrochloric acid. The solid that separated was collected and recrystallized from the proper solvent to give compound IIIe.

Effect of sodium ethoxide on (Ic): Formation of the ester IIIf. A solution of Ic (0.01 mole) and sodium ethoxide (0.015 mole) in ethanol (30 ml) was refluxed for 2 hrs. The reaction mixture after cooling was poured into ice/dil. hydrochloric acid. The solid that separated was crystallised from a suitable solvent, to furnish IIIe.

Reaction of m-toluidine with Ic: Formation of the imidazolone V. A solution of Ic (0.01 mole), *m*-toluidine (0.01 mole) and anhydrous sodium acetate (0.01 mole) in acetic acid (40 ml) was refluxed for 3 hrs. The solid that separated after concentration and cooling was crystallized from the proper solvent to give compound V.

Formation of VIa. A mixture of IIa (0.1 mole) and *m*-chloroaniline (0.1 mole) in ethanol (30 ml) was refluxed for 6 hrs and cooled. The solid that separated out was filtered off and recrystallized to give VIa.

Hydrolysis of IIa with aqueous alcoholic sodium hydroxide: Formation of VIb. A solution of (IIa) (0.01 mole) in ethanol (30 ml) was treated with sodium hydroxide (0.01 mole) in water (2 ml). The reaction mixture was refluxed for 3 hrs. After evaporation of most of the alcohol, the reaction mixture was diluted with water and acidified with dilute HCl. The solid that separated was collected and recrystallized to give VIb.

Fusion of IIb and/or IIc with benzylamine: Formation of imidazolones (VIIa and b). A mixture of IIb and/or IIc (0.01 mole) and benzylamine (0.01 mole) was heated at 170° in oil bath for 2 hrs. The solid product was collected and recrystallized to give VII_a and/or VII_b respectively.

Reaction of IIc with aniline in toluene; Formation of VIIc. A solution of IIc (0.1 mole), toluene (30 ml) and aniline (0.1 mole) was heated under reflux for 6 hrs, then cooled and the solid product that separated out was crystallized to give VIIc.

Aminolysis of (IId) with: 1 mole and 2 mole cyclohexyl amine: Formation of VII and VIII. A solution of IId (0.1 mole) in toluene was treated with cyclohexylamine (0.1 mole) and (0.2 mole) was heated under reflux for 6 hrs and then left to cool. The solid product was collected by filteration and recrystallized from toluene to give VIId (40% yield). The mother

liquor was left to slow evaporation and the solid product obtained was recrystallized from light petrol (60-80°) to yield VIII (35%) yield.

Hydrazinolysis of (IId): Formation of (IX, X, XI and XII). A solution of IId (0.01 mole) and (0.1 mole) in ethanol (50 ml) was treated with phenylhydrazine and the reaction mixture was heated under reflux for 6 hrs and left to cool. The solid product was collected by filtration and recrystallized from benzene to give (IX) and (XI) respectively. The mother liquor was evaporated to give a solid which offer recrystallization from petroleum ether (60-80°) gave (X) and (XII) respectively.

References

1. E. Erlenmeyer and E. Frustuck, Ann., **284**, 36 (1895).
2. A.F.M. Fahmy, A.A. Afifi and I.G. Shenouda, Revue Roumaine de Chimie, **24** (2), 373 (1979).
3. A.A. Afifi, M.A. El-Hashash and S.S. El-Kady, Revue Roumaine de Chimie, **28** (8), 848 (1983).
4. M.A. El-Hashash, A.A. Afifi, A.M. Kaddah and S.S. El-Kady, Synthesis, **10**, 798 (1981).