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Synthesis and Reactions of 1-(*p*-Tolyl)-5,6,7, 8-Tetrabromo-3,2-Benzoxazin-4-One

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The oxime's (2a-g) has been obtained from the reactions of titled compound (1) with benzylamine, *p*-toluidine, acetylhydrazide, salicylohydrazide and with aromatic and/or aliphatic hydrocarbons under Friedel-Crafts and Grignard reaction conditions. 3-Phthalazin-4-one derivatives (3a-h) and (4) has been obtained from the reactions of benzoxazone (1) with *p*-anisidine, benzoylhydrazide, cyclization product of oximes (2c and d) and from the reaction of (1) with hydrazine. Fusion of (1) with ammonium acetate and/or with phenylacetic acid leads to formation of phthalazinone (5a) and (6) respectively. Also reaction of compound (1) with P_2S_5 and active methylene compounds are described. The reaction of chlorophthalazine derivatives (5b) with nitrogen nucleophiles has been investigated.

INTRODUCTION

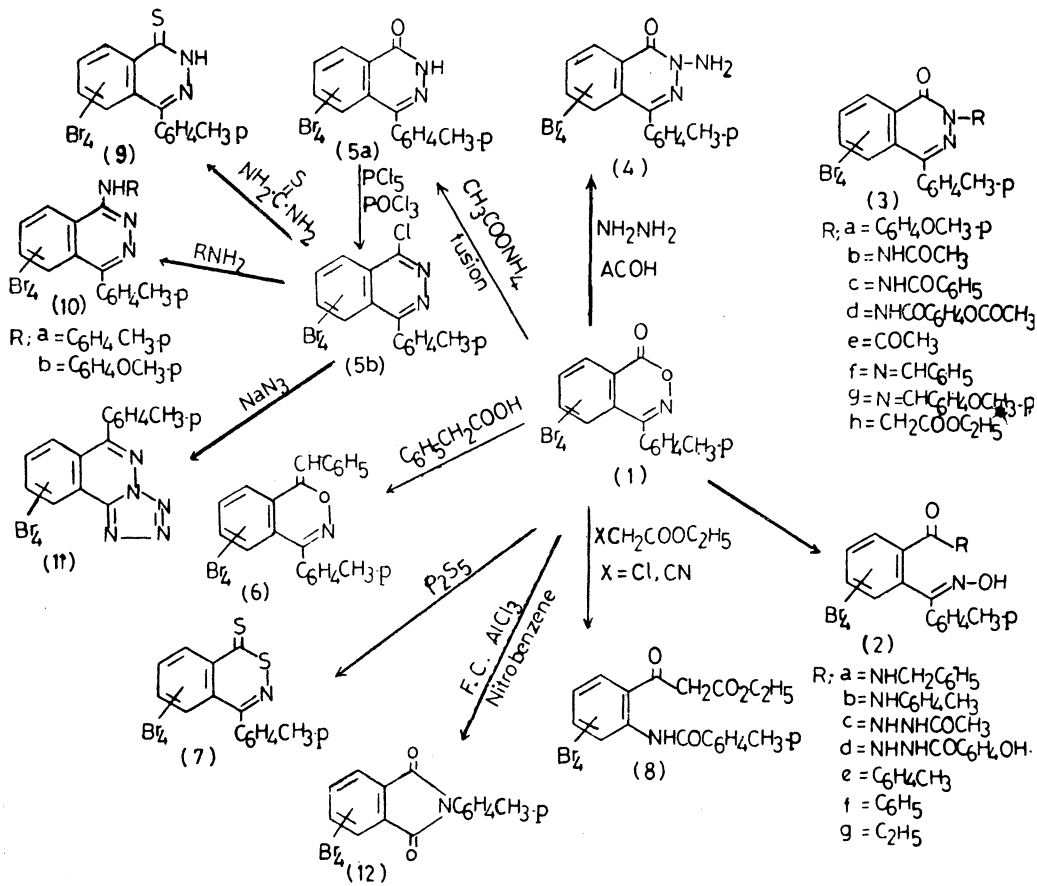
It has been reported[1] that 1-substituted-3,2-(4H)-benzoxazinone can be obtained by the reaction of *o*-aroylbenzoic acid with hydroxylamine. In the present investigation the author sought to prepare the titled compound with the aim of study its behaviour towards some nucleophiles. 1-(*p*-Tolyl)-5,6,7,8-tetrabromo-3,2-benzoxazin-4-one (1) has been prepared from ring closure of 2-toluoyl-3,4,5,6-tetrabromobenzoic acid with hydroxylamine in boiling pyridine, IR of (1) shows strong absorption band at 1740 cm^{-1} for δ-lactone and C=N at (1615 cm^{-1}).

It was mentioned that 2-substituted-3,1-benzoxazinone reacts with primary aromatic amines in boiling ethanol to give quinazolinone[2] and anthranilic acid anilides[2,3]. In the present work the author repeated this reaction using 1-substituted-3,2-benzoxazinone (1) with the aim of obtaining some precise information about the course of the reaction and on the other hand, to contrast the behaviour of 3,2-benzoxazinone and 3,1-benzoxazinone rings.

RESULTS AND DISCUSSION

Reaction of (1) with benzylamine, *p*-toluidine in boiling acetic acid ring opening occur and afforded the anilide (2a and b). IR of (2a and b) show $\nu_{C=O}$ (1710–1730 cm^{-1}) of anilide and in a range 3430–3410 cm^{-1} for ν_{OH} and ν_{NH}. In case of *p*-anisidine it gives phthalazine derivative (3a), IR of (3a) show $\nu_{C=O}$ at 1720 cm^{-1}.

Reaction of (1) with acid hydrazides such as acetyl and salicyloyl-hydrazide in boiling acetic acid gives the monoxieme derivatives (2c and d), but in case of benzoylhydrazide ring was opened followed by cyclization and yield the phthalazinone derivative (3c), IR of (2c and d) reveals



the presence of $\nu_{C=O}$ of hydrazide and aroyl ketone at (1700–1670 cm^{-1}), (1720–1710 cm^{-1}), two $\nu_{NH's}$ at (3320, 3240 cm^{-1}), ν_{OH} at 3500 cm^{-1}, in case of (3c) it shows absorption at 1650 cm^{-1} due to ν_{max} of carbonyl group, ν_{NH} at 3200 cm^{-1}.

Also compound (3c) has been synthesised via unambiguous route by treatment of 3-aminophthalazione with benzoyl chloride which gives compound identified as (3c) via m.pt. and mixed m.pt. determination.

Cyclization of (2c and d) with Ac_2O gave phthalazinone derivatives (3b and d). Structure of (3b) was confirmed authentically via interaction of aminophthalazinone (4) with Ac_2O which gives compound identified as

(3b) via m.pt. and mixed m.pt., on the other hand, compound (3d) not give violet colour with $FeCl_3$, IR spectra of (3b and d) show strong absorption bands at (1730, 1700, 1670 cm^{-1}) attributable to ν_{max} of two carbonyl groups and $\nu_{C=N}$, $\nu_{NH's}$ at (3320, 3240cm^{-1}).

It's well known that benzoxazine derivatives[2,3] undergo hetero ring opening with aromatic hydrocarbon under Friedel-Craft's condition. In this investigation the author extended such reaction to include reaction of compound (1) with aromatic hydrocarbons. Thus when benzoxazinone (1) reacts with benzene and/or toluene in presence of anhydrous $AlCl_3$ and gives benzophenone derivative (2e and f) which shows $\nu_{C=O}$ at (1690 cm^{-1}), broad band for ν_{OH} at 3440–3400 cm^{-1}.

Benzoxazinone (1) reacts with anhydrous $AlCl_3$ in presence of hot nitrobenzene, to give the corresponding N-tolyl tetrabromophthalimide (12). Compound (12) also obtained from the fusion reaction of *p*-toluidine with tetrabromophthalic acid.

Also it was mentioned that 2,3-benzoxazin-1-one and its 4-aryl or acyl derivatives[4–6] react with phenylmagnesium bromide to give the corresponding oximes of triphenylcarbinol where ring opening reaction occur. When 3,2-benzoxazin-4-one react with alkyl or arylmagnesium halide under Grignard reactions conditions to give the corresponding oxime. Thus when compound (1) allowed to react with ethylmagnesium iodids and/or phenylmagnesium bromide oximes (2f and g) were obtained, its IR spectra shows $\nu_{C=O}$ at 1700 cm^{-1} broad band of ν_{OH} at 3440–3350 cm^{-1}.

It is reported that 2-substituted-3,1-benzoxazinone reacts with hydrazine hydrate in boiling ethanol yielded anthranilic acid hydrazide[2] or quinazolinones[3,7,8]. Thus when compound (1) was allowed to react with hydrazine hydrate in boiling acetic acid leads to formation of 3-aminophthalazinone (4) via ring opening reaction followed by cyclization. IR of (4) shows strong absorption band at 1700 cm^{-1} for carbonyl, at 1610 cm^{-1} for $\nu_{C=N}$ and at (3340, 3220 cm^{-1}) for two $\nu_{NH's}$.

When 2-substituted-3,1-benzoxazinone was submitted to react with boiling alcoholic ammonia resulting in formation of anthranilamide[2]. In this work compound (1) was reacted with ammonium acetate at 170°C and the product was proved to be phthalazinone (5a), it's IR show strong absorption band at 1715 cm^{-1} for $\nu_{C=O}$, at 3240 cm^{-1} for ν_{NH}. Acetylation of (5a) with Ac_2O gives (3e). It was mentioned that 3-aminoquinazoline[8], condensed with aromatic aldehydes and yielded Schiff bases. In this work the author extended such reaction to include the reaction of 3-aminophthalazinone (4) with benzaldehyde and anisaldehyde by fusion to give condensed product (3f and g). IR of (3f and g) shows $\nu_{C=O}$ at (1720–1690 cm^{-1}), $\nu_{C=N}$ at (1600, 1590 cm^{-1}) respectively.

It was reported[9] that when 2-*iso*propyl-3,1-benzoxazin-4-one reacted with P_2S_5 in boiling xylene afforded the corresponding thione derivative,

but when (1) react with P_2S_5 in dry xylene yielded the corresponding benzothiazin-4-thione (7). The assigned structure was supported from IR spectrum which showed bands attributable to $\nu_{C=N}$ at (1600 cm^{-1}) and $\nu_{C=S}$ at (1330 cm^{-1}).

It was mentioned that 3,1-benzoxazinone reacts with active methylene compounds[2] as ethyl acetoacetate, diethyl malonate and ethyl cyanoacetate to give one and the same product, ethyl 2-benzamide benzoyl acetate, the same behaviour was observed when compound (1) reacts with ethyl chloroacetate and/or ethyl cyanoacetate in boiling dry pyridine and yielded 2-benzamide benzoyl acetate (8). IR spectra shows three carbonyl groups at (1715, 1690 and 1670 cm^{-1}). 1-(*p*-Tolyl)-4-chloro-5,6,7,8-tetrabromophthalazine (5b) reacts with thiourea by fusion to give phthalazin-4-thione(9). IR spectrum of (9) shows that it exists as thione $\rightleftharpoons$ thiol tautomers, IR shows a broad band in range 3330–3250 cm^{-1} for ν_{NH} and ν_{SH}, $\nu_{C=S}$ at 1750 cm^{-1}. Also 4-chlorophthalazine (5b) reacts by fusion with *p*-toluidine and/or *p*-anisidine to give the corresponding secondary amines (10a and b). IR shows that ν_{NH} of secondary amine at 3400 cm^{-1}. When sodium azide allowed to react with 4-chlorophthalazine in boiling ethanol according to Stolle reaction it yielded the tetrazole compound (II). It's IR shows three $\nu_{N=N}$ band at 1560, 1530, 1500 cm^{-1}.

EXPERIMENTAL

The melting points reported are uncorrected. IR spectra in KBr were recorded on a Unicam Sp 1200 spectrophotometer.

(i) 1-(p-Tolyl-5,6,7,8-tetrabromo-3,2-benzoxazine-4-one (1)

A solution of 2-toluoyl-3,4,5,6-tetrabromobenzoic acid (0.01 mole) in pyridine (30 ml) was refluxed with (0.02 mole) of hydroxylamine hydrochloride for 4 hrs, pour on ice/HCl, filtered off, washed with water and crystallized from n-butanol.

(ii) Action of primary amines, acid hydrazides and hydrazine hydrate on 3,2-benzoxazinone (1): Formation of (2a–d), (3c) and (4)

(0.005 Mole) of (1) refluxed in 50 ml acetic acid with amines (0.01 mole) namely *p*-toluidine, benzylamine, *p*-anisidine or acid hydrazides (acetyl hydrazide, salicyloyl hydrazide and benzoyl hydrazide or with hydrazine hydrate for ½ hr, then cooled, poured on ice/HCl, filtered, wash with water, crystallized from a suitable solvent [cf. Table (1)].

(iii) Friedel-Crafts alkylation of benzoxazinone (1): Formation of (2e and f)

To a solution of (1) (0.005 mole) in toluene (50 ml), aluminium chloride (0.04 mole) was added with stirring a vigorous evolution of hydrogen chloride, took place, stirring was continued for an additional ½ hr,

TABLE 1

PHYSICAL DATA OF VARIOUS COMPOUNDS PREPARED

Compd	M. pt. °C Solvent	Yield %	Mol. Formula	Analysis % Calcd/Found		
				C	H	N
1	> 330 (n-butanol)	90	$C_{15}H_7NO_2Br_4$	32.27 32.1	1.27 1.3	2.53 2.4
2a	210 (AcOH)	92	$C_{22}H_{16}N_2O_2Br_4$	40.02 39.7	2.43 2.4	4.25 4.1
2b	261 (AcOH)	85	$C_{22}H_{16}N_2O_2Br_4$	40.02 39.7	2.43 2.4	4.25 4.1
2c	288 (AcOH)	70	$C_{17}H_3O_3Br_4$	32.55 32.6	2.07 2.0	6.7 6.7
2d	275 (nitrobenzene)	75	$C_{22}H_{15}N_3O_4Br_4$	37.47 37.7	2.13 2.1	5.96 5.8
2e	195 (xylene)	83	$C_{22}H_{15}NO_2Br_4$	40.96 41.1	2.33 2.2	2.17 2.2
2f	95 pet. ether (60–80)	20	$C_{21}H_{13}NO_2Br_4$	39.96 39.9	2.06 2.1	2.22 2.2
2g	98 pet. ether	20	$C_{17}H_{13}NO_2Br_4$	35.01 35.0	2.23 2.2	2.40 2.3
3a	185 (n-butanol)	90	$C_{22}H_{14}N_2O_2Br_4$	40.15 40.0	2.13 2.0	4.26 4.4
3b	185 (nitrobenzene)	85	$C_{17}H_4N_3O_2Br_4$	33.55 33.3	1.8 1.7	6.9 7.1
3c	270 (nitrobenzene)	70	$C_{22}H_{13}N_3O_2Br_4$	39.37 39.1	1.94 1.9	6.26 5.9
3d	236 (nitrobenzene)	72	$C_{22}H_{13}N_3O_3Br_4$	40.4 40.5	2.1 2.2	5.9 5.9
3e	195 (AcOH)	90	$C_{17}H_{10}N_2O_2Br_4$	34.37 34.7	1.69 1.6	4.72 4.9
3f	270 (AcOH)	85	$C_{22}H_{13}N_3OBr_4$	40.33 40.0	1.99 2.1	6.42 6.3
3g	215 (AcOH)	75	$C_{23}H_{15}N_3O_2Br_4$	40.32 40.1	2.19 2.2	6.14 5.9
3h	198–200 alcohol	60	$C_{19}H_{14}N_2O_3Br_4$	35.76 35.9	2.2 2.2	4.39 4.3
4	> 330 (n-butanol)	90	$C_{15}H_9N_3OBr_4$	31.77 31.9	1.59 1.6	7.41 7.7

Table 1 (contd,)

Compd	M. pt. °C Solvent	Yield %	Mol. Formula	Analysis % Calcd/Found		
				C	H	N
5	> 330 (n-butanol)	80	$C_{15}H_8N_2OBr_4$	32.63 33.0	1.45 1.5	5.08 5.0
6	235 (n-butanol)	85	$C_{22}H_{13}NOBr_4$	42.13 41.9	2.1 2.0	2.23 2.1
7	295 (xylene)	60	$C_{15}H_7NS_2Br_4$	30.79 31.0	1.2 1.2	2.2 2.2
8	223 ethanol	70	$C_{19}H_{15}NO_4Br_4$	35.59 35.6	2.34 2.2	2.18 2.0
9	> 330 AcOH	70	$C_{15}H_8N_2SBr_4$	31.71 31.5	1.41 1.4	4.93 5.1
10a	260 ethanol	75	$C_{22}H_{15}N_3Br_4$	41.21 41.2	2.34 2.5	6.55 6.5
10b	240 ethanol	80	$C_{22}H_{15}N_3OBr_4$	40.2 40.0	2.28 2.3	6.39 6.4
11	> 330 AcOH	70	$C_{15}H_7N_5Br_4$	31.22 31.3	1.21 1.2	12.14 12.1

refluxed the complex for 3 hrs on water bath, poured to ice/HCl then steam-distilled to remove excess toluene, filtered, crystallized from xylene.

(iv) Action of Grignard reagents on benzoxazinone (1): formation of (2f and g)

In dry ether (50 ml), (0.005 mole) of (1) was treated with Grignard reagent (0.03 mole) in 50 ml in dry ether for 1/2 hr, the reaction mixture was then heated under reflux for 4 hrs, left overnight at room temperature and decomposed in the usual way. The ethereal layer was separated, dehydrated over anhydrous sodium sulphate and the solvent distilled off, crystallization from pet. ether 60-80°C.

(v) Acetylation of 3-aminophthalazin-4-one (4): Formation of (3b)

(0.005 Mole) of (4) was refluxed with acetic anhydride (10 ml) for 2 hrs then cool, filter, crystallized from suitable solvents.

(vi) Benzoylation of 3-aminophthalazinone (4): Formation of (3c)

(0.005 Mole) of (4) was heated with (0.01 mole) of benzoyl chloride in boiling benzene (20 ml) for 2 hrs then cool, filter, crystallized from suitable solvent.

(vii) *Condensation* of (4) with aromatic aldedhydes: Formation of Schiff's bases (3f and g)

(0.005 Mole) of (4) was fused with (0.02 mole) of benzaldehyde or anisaldehyde on oil bath at 170°C in presence of air condenser for 3 hrs then the product was crystallized from acetic acid.

(viii) Conversion of benzoxazinone (1) into phthalazinone (5a)

(0.005 Mole) of (1) was fused with (0.05 mole) ammonium acetate on oil bath at 170°C in presence of air condenser for 3 hrs then cooled, water is added. The solid obtained was crystallized from *n*-butanol.

(ix) Action of ethyl chloroacetate on phthalazine-4-one (5a): Formation of (3h)

A mixture of (5a) (0.005 mole) and ethyl chloroacetate (0.03 mole) in dry pyridine (40 ml) was heated under reflux for 4 hrs, poured into cold dilute HCl, and the solid obtained was filtered and recrystallized from ethanol.

(x) Action of phenylacetic acid on benzoxazinone (1): Formation of (6)

(0.005 Mole) of (1) was fused with (0.02 mole) of phenylacetic acid on oil bath at 170°C for 3 hrs in presence of air condenser, the product obtained treated with water then crystallized from *n*-butanol.

(xi) Action of phosphorous pentasulphide on benzoxazinone (1): Formation of (7)

A solution of (1) (0.005 mole) and P_2S_5 (0.02 mole) in 50 ml of dry xylene was heated under reflux for 1 hr. The reaction mixture was filtered while hot and the product crystallized from xylene.

(xii) Action of ethyl chloroacetate and/or ethyl cyanoacetate on benzoxazinone (1): Formation of (8)

A mixture of (1) (0.005 mole) and ethyl chloroacetate or ethyl cyanoacetate (0.03 mole) in dry pyridine (40 ml) was heated under reflux for 4 hrs, poured into cold dilute HCl, and the solid obtained crystallized from acetic acid.

(xiii) Fusion of chlorophthalazine (5b) and thiourea: Formation of phthalazine thione (9)

A mixture of (5b) (0.005 mole) of chlorophthalazine and (0.03 mole) of thiourea were heated on sand bath above the melting point for 3 hrs in presence of air condenser. The solid obtained treated with ethyl alcohol on cold, and crystallized from acetic acid.

(xiv) Fusion of chlorophthalazine (5b) and p-toluidine and/or p-anisidine: Formation of (10a and b)

A mixture of (0.005 mole) of (5b) and (0.03 mole) of amine was heated above the melting point on oil bath for 3 hrs the solid obtained treated with dilute HCl, and crystallized from suitable solvent.

(xv) Action of sodium azide on chlorophthalazine (5b): Formation of tetrazole (11)

A mixture of (0.005 mole) of (5b) and sodium azide (0.02 mole) in boiling ethanol (40 ml) was refluxed for 2 hrs concentrated and poured into water, the precipitate thus obtained was filtered and crystallized from acetic acid.

(xvi) Action of $AlCl_3$ on benzoxazinone (1) in presence of nitrobenzene: Formation of (12)

To a solution of (1) (0.005 mole) in dry nitrobenzene (40 ml), anhydrous $AlCl_3$ (0.05 mole) was added with stirring, then reflux for 1/4 hr, pour on ice/HCl, solvent steam distilled and crystallized from ethyl alcohol.

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