Synthesis and Reactions of 5,6,7,8-Tetrabromo-4-(3,4-dimethylphenyl)-1*H*-2,3-benzoxazin-1-one

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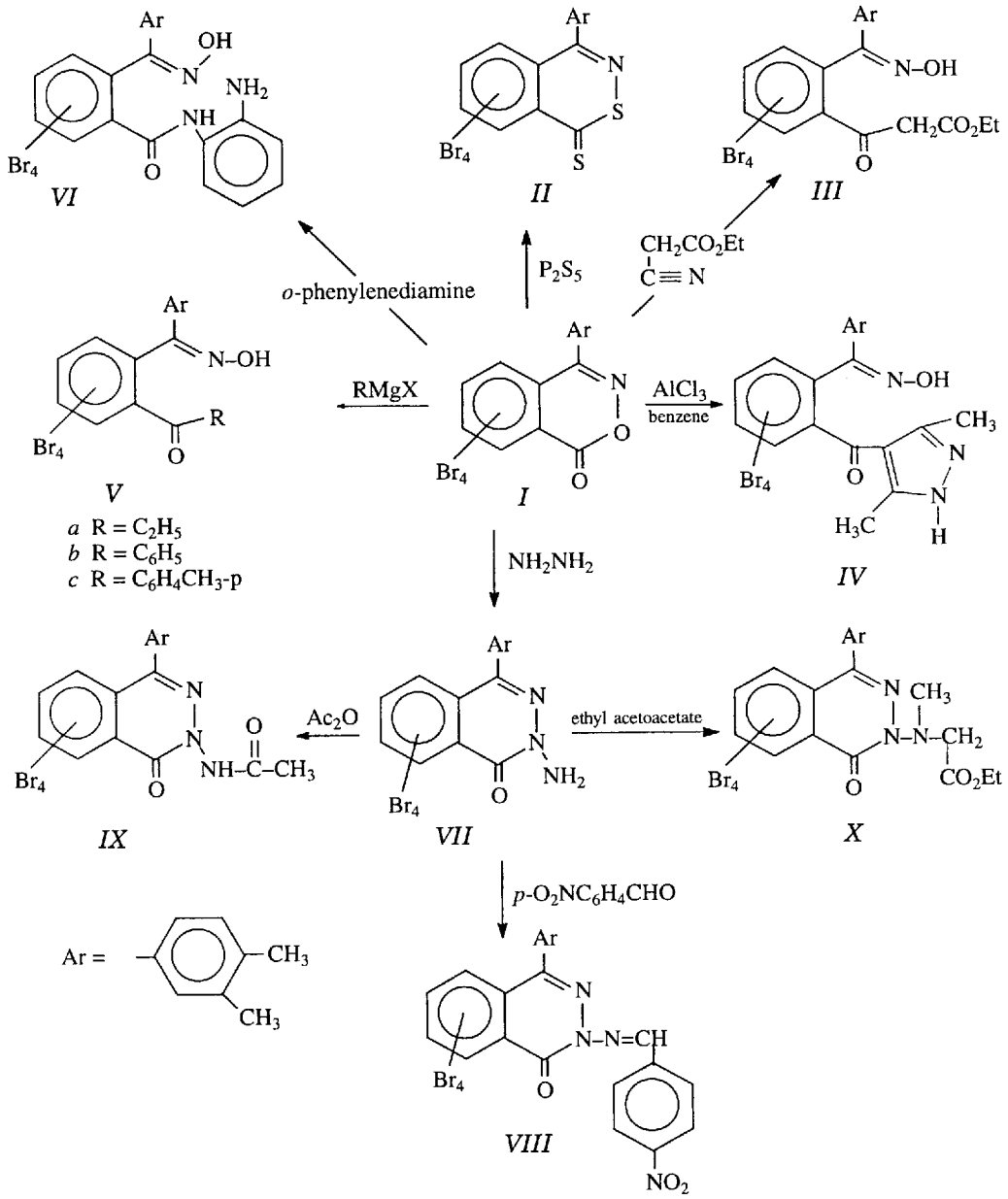
The behaviour of 5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1*H*-2,3-benzoxazin-1-one towards phosphorus pentasulfide, active methylene compounds, 3,5-dimethylpyrazole under Friedel—Craft's conditions, Grignard reagents, *o*-phenylenediamine, and hydrazine hydrate has been investigated. Also, reactions of 2-amino-5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-2*H*-phthalazin-1-one with aromatic aldehyde, acetic anhydride, and ethyl acetate are described.

The previous studies of the hetero ring opening of 4*H*-3,1-benzoxazin-4-one [1, 2] and chemical reactivity of phthalazinone derivative [3] promoted the interest for the synthesis of 1*H*-2,3-benzoxazin-1-one derivatives. So, the present work investigated the behaviour of 5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1*H*-2,3-benzoxazin-1-one (*I*) towards sulfur, carbon, and nitrogen nucleophiles. Interaction of compound *I* with phosphorus pentasulfide in boiling xylene yields 5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)thiazine-1-thione (*II*) (Scheme 1) which is used to investigate stability and behaviour of the heteroaryl moiety in the benzoxazinone ring. Thus, reaction of compound *I* with ethyl cyanoacetate in boiling ethanol in the presence of sodium ethoxide [4] under Claisen reaction conditions gave ethyl 3-oxo-3-[2,3,4,5-tetrabromo-6-(3,4-dimethylphenyl-hydroxyiminomethyl)phenyl]propionate (*III*). The formation of *III* can be explained by opening the heterocyclic ring with carbanion derived from ethyl cyanoacetate forming fleeting intermediate, which was followed by elimination of hydrogen cyanide. Recently, reaction of 2-ethoxycarbonyl-4*H*-3,1-benzoxazin-4-one with 3,5-dimethylpyrazole under Friedel—Craft's conditions has been investigated [5]. Thus, when compound *I* was allowed to react with 3,5-dimethylpyrazole in the presence of anhydrous aluminium chloride in dry benzene it afforded (3,5-dimethyl-1*H*-pyrazol-4-yl)-[2,3,4,5-tetrabromo-6-(3,4-dimethylphenyl-hydroxyiminomethyl)-phenyl]methanone (*IV*). It has been reported [6] that 2-cyanomethyl-4*H*-3,1-benzoxazine underwent hetero ring opening by interaction with Grignard reagent. Similarly, compound *I* was reacted with ethylmagnesium bromide, phenylmagnesium bromide, and *p*-tolylmagnesium bromide and yielded 3,4-dimethylphenyl-[2,3,4,5-tetrabromo-6-(propionyl)phenyl]-(*Va*), 3,4-dimethylphenyl-(2,3,4,5-tetrabromo-6-benzoylphenyl)-methanone oxime (*Vb*), and 3,4-dimethylphenyl-[2,3,4,5-tetrabromo-6-(4-methylbenzoyl)phenyl]methanone oxime (*Vc*), respectively. The interaction of 3,2-benzoxazinone derivative with anthranilic acid gave the corresponding compound in which occurs hetero ring opening [7]. So, compound *I* reacted with *o*-phenylenediamine in boiling butanol and furnished *N*-(2-aminophenyl)-2,3,4,5-tetrabromo-6-(3,4-dimethylphenyl-hydroxyiminomethyl)benzamide (*VI*). Previously, it was reported [8—10] that the reaction of 4*H*-3,1-benzoxazine-4-one with hydrazine hydrate effects the fission of heterocyclic ring. This prompted the study of the behaviour of compound *I*, which contains two reactive centres towards hydrazine hydrate. Thus, compound *I* was allowed to react with hydrazine hydrate in boiling ethanol and afforded 2-amino-5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-2*H*-phthalazin-1-one (*VII*). When the phthalazinone *VII* reacted with *p*-nitrobenzaldehyde in boiling ethanol [11,12], it yielded 5,6,7,8-tetrabromo-2-[(4-nitrobenzylidene)amino]-4-(3,4-dimethylphenyl)-2*H*-phthalazin-1-one (*VIII*). Also, compound *VII* was allowed to react with boiling acetic anhydride yielding *N*-[5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1-oxo-2*H*-phthalazin-2-yl]acetamide (*IX*). On the other hand, compound *VII* was condensed with ethyl acetoacetate in absolute ethanol [13] and produced 5,6,7,8-tetrabromo-2-[*N*-methyl-*N*-(ethoxycarbonylmethyl)amino]-4-(3,4-dimethylphenyl)-2*H*-phthalazin-1-one (*X*).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were measured on Perkin—Elmer 398 spectrophotometer. The ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz instrument using DMSO-d_6—$CDCl_3$ as solvent and TMS as internal reference. The microanalysis was preformed using the Perkin—Elmer 2400 CHN analyzer.



Scheme 1

5,6,7,8-Tetrabromo-4-(3,4-dimethylphenyl)-1*H*-2,3-benzoxazin-1-one (*I*)

A mixture of 2,3,4,5-tetrabromo-6-(3,4-dimethylbenzoyl)benzoic acid (0.01 mol) and hydroxylammonium chloride (0.01 mol) in pyridine (30 cm^3) was refluxed for 3 h. The solid that separated after concentration and cooling was crystallized from ethanol. Yield 75 %, m.p. = 223 °C. For $C_{16}H_9Br_4NO_4$ (M_r = 483) w_i(calc.): 33.86 % C, 1.59 % H, 2.47 % N; w_i(found): 33.70 % C, 1.50 % H, 2.40 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1755 ν(C=O), 1630 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ: 2.15—2.25 (d, 6H, $2CH_{3\ arom}$), 6.9—7.6 (m, 3H, H_{arom}).

5,6,7,8-Tetrabromo-4-(3,4-dimethylphenyl)thiazine-1-thione (*II*)

A solution of *I* (0.01 mol) and phosphorus pentasulfide (0.02 mol) in dry xylene (30 cm^3) was refluxed for 30 min. The reaction mixture was filtrated at hot. The obtained solid was crystallized from xylene. Yield 57 %, m.p. = 205 °C. For $C_{16}H_9NBr_4S_2$ (M_r = 599) w_i (calc.): 32.05 % C, 1.50 % H, 2.34 % N; w_i(found): 32.00 % C, 1.45 % H, 2.24 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 675—690 ν(C—S), 1175—1190 ν(C=S), 1630 ν(C=N). ^1H NMR spectrum (DMSO-d_6), δ: 2.1 (s, 3H, p-$CH_{3\ arom}$), 2.25 (s, 3H, m-$CH_{3\ arom}$), 6.7—7.4 (m, 3H, H_{arom}).

Ethyl 3-Oxo-3-[2,3,4,5-tetrabromo-6-(3,4-dimethylphenyl-hydroxyiminomethyl)-phenyl]propionate (*III*)

A solution of *I* (0.01 mol) and ethyl cyanoacetate (0.03 mol) in sodium ethoxide (30 cm^3) was refluxed for 4 h on a steam bath. The excess alcohol was removed, then poured onto ice—HCl. The obtained solid was crystallized from benzene. Yield 60 %, m.p. = 172 °C. For $C_{20}H_{17}Br_4NO_4$ (M_r = 655) w_i(calc.): 36.64 % C, 2.60 % H, 2.14 % N; w_i(found): 36.50 % C, 2.6 % H, 2.10 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1630 ν(C=N), 1670 ν(C=O of ketone), 1740 ν(C=O of ester), 3350 ν(OH). ^1H NMR spectrum (DMSO-d_6), δ: 2.1 (t, 3H, CH_2—CH_3), 2.2 (s, 2H, CH_2CO), 4.2 (q, 2H, CH_2 of ester), 7.1—7.8 (m, 3H, H_{arom}), 9.1 (s, 1H, OH). Mass spectrum, *m/z* (I_r/%): 655 (0.01) (M^+), 582 (0.04), 568 (0.10), 540 (0.70), 523 (1.13), 392 (1.49), 131 (2.87),107 (10.62),105 (100.00), 78 (16.76).

(3,5-Dimethyl-1*H*-pyrazol-4-yl)-[2,3,4,5-tetrabromo-6-(3,4-dimethylphenyl-hydroxyiminomethyl)phenyl]methanone (*IV*)

A solution of *I* (0.01 mol) and 3,5-dimethylpyrazole (0.01 mol) in dry benzene (30 cm^3) and anhydrous aluminium chloride (0.03 mol) was stirred and heated on a water bath for 6 h. The reaction mixture was decomposed with ice-cold hydrochloric acid. The excess benzene was removed and the residual semisolid was extracted with ether. The solid product was crystallized from benzene. Yield 70 %, m.p. = 189 °C. For $C_{21}H_{17}Br_4N_3O_2$ (M_r = 663) w_i(calc): 38.01 % C, 2.56 % H, 6.33 % N; w_i(found): 37.90 % C, 2.50 % H, 6.30 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1620 ν(C=N), 1670 ν(C=O of ketone), 3240 ν(NH), 3350 ν(OH). ^1H NMR spectrum (DMSO-d_6), δ: 2.0—2.15 (d, 6H, $2CH_{3\ arom}$), 2.25 (s, 3H, CH_3NH), 2.35 (s, 3H, CH_3—C=N), 5.3 (s, 1H, NH), 7.4—7.9 (m, 3H, H_{arom}), 9.2 (s, 1H, OH).

3,4-Dimethylphenyl-[2,3,4,5-tetrabromo-6-(propionyl)phenyl]- (*Va*), 3,4-Dimethylphenyl-(2,3,4,5-tetrabromo-6-benzoylphenyl)methanone Oxime (*Vb*), and 3,4-Dimethylphenyl-[2,3,4,5-tetrabromo-6-(4-methylbenzoyl)-phenyl]methanone Oxime (*Vc*)

A solution of *I* (0.01 mol) and an ethereal solution of Grignard reagents was treated in dry xylene (30 cm^3) for 30 min. The reaction mixture was heated under reflux for 6 h, left overnight at room temperature and then decomposed in the usual way. The obtained products were crystallized from the benzene. Yield of *Va* 70 %, m.p. = 170 °C. For $C_{18}H_{15}Br_4NO_2$ (M_r = 597) w_i(calc): 36.18 % C, 2.51 % H, 2.35 % N; w_i(found): 36.10 % C, 2.40 % H, 2.30 % N. Yield of *Vb* 60 %, m.p. = 192 °C. For $C_{22}H_{15}Br_4NO_2$ (M_r = 645) w_i(calc.): 40.93 % C, 2.33 % H, 2.17 % N; w_i(found): 40.80 % C, 2.20 % H, 2.10 % N. Yield of *Vc* 55 %, m.p. = 235 °C. For $C_{23}H_{17}Br_4NO_2$ (M_r = 659) w_i(calc.): 41.88 % C, 2.58 % H, 2.12 % N; w_i(found): 41.70 % C, 2.50 % H, 2.10 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1630 ν(C=N), 1675 ν(C=O), 3350 ν(OH). ^1H NMR spectrum of *Va* (DMSO-d_6), δ: 1.3 (t, 3H), 2.1 (q, 2H, for propiophenone moiety), 2.15—2.35 (d, 6H, $2CH_{3\ arom}$), 7.6—7.9 (m, 3H, H_{arom}), 9.1 (s, 1H, OH); *Vc*: 2.15—2.30 (d, 9H, $3CH_{3\ arom}$), 7.4—8.1 (m, 7H, H_{arom}), 9.1 (s, 1H, OH). Mass spectrum of *Va*, *m/z* (I_r/%): 597 (0.20) (M^+), 569 (0.75), 568 (0.35), 540 (0.97), 523 (1.69), 392 (3.67),181 (5.70), 93 (100.00), 91 (39.61), 90 (7.96).

***N*-(2-Aminophenyl)-2,3,4,5-tetrabromo-6-(3,4-dimethylphenyl-hydroxyiminomethyl)-benzamide (*VI*)**

A solution of *I* (0.01 mol) and *o*-phenylenediamine (0.01 mol) in butanol was refluxed for 12 h. The obtained solid after cooling was crystallized from ethanol. Yield 75 %, m.p. = 241 °C. For $C_{22}H_{17}Br_4N_3O_2$ (M_r = 675) w_i(calc.): 39.11 % C, 2.52 % H, 6.22 % N; w_i(found): 39.01 % C, 2.40 % H, 6.12 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1620 ν(C=N), 1660 ν(CONH), 3200—3240 ν(NH), 3340 ν(OH). ^1H NMR spectrum of *Va* (DMSO-d_6), δ: 2.1 (s, 3H, *p*-$CH_{3\ arom}$), 2.3 (s, 3H, *m*-$CH_{3\ arom}$), 5.3 (s, 2H, 2NH), 7.3—7.9 (m, 7H, H_{arom}), 9.2 (s, 1H, OH).

2-Amino-5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-2*H*-phthalazin-1-one (*VII*)

A solution of *I* (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 cm^3) was refluxed for 3 h and the reaction mixture was concentrated and cooled, then the solid was crystallized from ethanol. Yield 60 %, m.p. = 178 °C. For $C_{16}H_{11}Br_4N_3O$ (M_r = 581) w_i(calc.): 33.05 % C, 1.89 % H, 7.23 % N; w_i(found): 33.00 % C, 1.85 % H, 7.20 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1630 ν(C=N), 1665 ν(C=O of cyclic carboxamide), 3230 ν(NH). ^1H NMR spectrum (DMSO-d_6), δ: 2.1—2.25 (d, 6H, $2CH_{3\ arom}$), 5.1 (s, 1H, NH), 7.0—7.6 (m, 7H, H_{arom}). Mass spectrum, *m/z* (I_r/%): 581 (0.03) (M^+), 538 (0.21), 537 (2.86), 509 (9.67), 392 (100.00), 133 (39.17), 107 (13.96), 105 (22.30), 78 (16.90).

5,6,7,8-Tetrabromo-2-[(4-nitrobenzylidene)amino]-4-(3,4-dimethylphenyl)-2*H*-phthalazin-1-one (*VIII*)

A solution of *VII* (0.01 mol) and 4-nitrobenzaldehyde (0.01 mol) in ethanol (30 cm^3) was heated under reflux for 6 h. The solid that separated on cooling was crystallized from ethanol. Yield 62 %, m.p. = 217 °C. For $C_{23}H_{14}Br_4N_4O$ (M_r = 714) w_i(calc.): 56.30 % C, 2.05 % H, 8.21 % N; w_i(found): 56.20 % C, 2.00 % H, 8.10 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1620 ν(C=N), 1360 ν(NO_2), 1670 ν(C=O of cyclic amide), and lacking absorption of NH. ^1H NMR spectrum (DMSO-d_6), δ: 2.1—2.3 (d, 6H, *p*-$CH_{3\ arom}$), 6.5 (s, 1H, olefinic proton), 7.1—7.7 (m, 7H, H_{arom}).

N-[5,6,7,8-Tetrabromo-4-(3,4-dimethylphenyl)-1-oxo-2*H*-phthalazin-2-yl]acetamide (*IX*)

A solution of *VII* (0.01 mol) and acetic anhydride (30 cm^3) was refluxed for 4 h. The reaction mixture was cooled and poured on water. The separated solid product was crystallized from benzene. Yield 73 %, m.p. = 195 °C. For $C_{18}H_{13}Br_4N_3O_2$ (M_r = 623) w_i(calc.): 34.67 % C, 2.09 % H, 6.74 % N; w_i(found): 34.50 % C, 1.90 % H, 6.60 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1650, 1670, 3250 due to $\tilde{\nu}$ of two carbonyl groups and NH, respectively. ^1H NMR spectrum (DMSO-d_6), δ: 2.1 (s, 3H, $\underline{CH_3}CO$), 2.25—2.35 (d, 6H, $2CH_{3\,arom}$), 6.4 (s, 1H, olefinic proton), 7.6—8.1 (m, 3H, H_{arom}).

5,6,7,8-Tetrabromo-2-[*N*-methyl-*N*-(ethoxycarbonylmethyl)amino]-4-(3,4-dimethylphenyl)-2*H*-phthalazin-1-one (*X*)

A solution of *VII* (0.01 mol) and ethyl acetoacetate (0.01 mol) was refluxed in absolute ethanol (30 cm^3) for 5 h. The reaction mixture was allowed to cool and the formed solid was filtered off and crystallized from ethanol. Yield 75 %, m.p. = 162 °C. For $C_{21}H_{17}Br_4N_3O_3$ (M_r = 693) w_i(calc.): 37.11 % C, 2.50 % H, 6.19 % N; w_i(found): 36.90 % C, 2.4 % H, 6.10 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 1620 ν(C=N), 1670 ν(C=O of cyclic amide), 1735 ν(C=O of ester) and lacking absorption of NH. ^1H NMR spectrum (DMSO-d_6), δ: 1.3 (s, 3H, $\underline{CH_3}CH_2$), 2.0 (s, 3H, CH_3), 2.15—2.30 (d, 6H, $2CH_{3\,arom}$), 3.2 (s, 2H, CH_2CO), 4.2 (q, 2H, $\underline{CH_2}CH_3$), 7.3—7.8 (m, 3H, H_{arom}).

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