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Some Reactions With 6-Bromo-2-phenyl-3,1-benzoxazin-4-one

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Abstract. 6-Bromo-2-phenyl-3,1-benzoxazin-4-one (1) reacts with benzylamine, aniline or morpholine via ring-opening to give the corresponding benzamide derivatives (2-4). The reaction of (1) with hydrazine hydrate in ethanol gave the benzhydrazide derivative (5) while their reaction in glacial acetic acid containing catalytic amount of fused sodium acetate yielded 3-acetylamino-6-bromo-2-phenylquinazolin-4-one (6). The latter compound was obtained on refluxing the hydrazide (5) with acetic anhydride for one hour. 6-Bromo-3-p-methoxybenzylideneamino-2-phenylquinazolin-4-one (7) was formed from the reaction of the hydrazide (5) with p-methoxybenzaldehyde. The reaction of (1) with phenylmagnesium bromide and benzylmagnesium chloride yielded the corresponding carbinols (9 & 10). The tetrazolyl acid derivative (11) was formed from the reaction of (1) with hydrazoic acid.

The reaction of 3,1-benzoxazin-4-ones with amines have been the subject of much study and controversy. Errede et al(1-5) reported that reaction of 6-bromo-2-methyl-3,1-benzoxazin-4-one with simple primary amines gave the corresponding quinazolin-4-ones via the intermediate formation of amidine salt (nucleophilic attack at position 2-) whereas reaction with secondary amines and bulky primary amines gave the corresponding ortho-substituted benzamides (nucelophilic attack at position 4-).

Contrary to Errede's postulations, Ismail et al(6) reported that the reaction of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one with amines gave entirely the benzamide derivatives formed by nucleophilic attack at position 4-. This shows that there is a marked difference in the behaviour of 6-bromo- and 6,8-dibromo-2-methyl-3,1-benzoxazin-4-ones towards amines. Recently, Ismail et al(7) reported that the reaction of 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one with amines involved also attack at position-4 forming benzamide derivatives. It seemed of interest to extend the previous work on 3,1-benzoxazin-4-ones(8-12) carried out in this laboratory to involve a study for the reactivity of 6-bromo-2-phenyl-3,1-benzoxazin-4-one (1) towards different nucleophilic reagents. When (1) was allowed to react with primary amines such as benzylamine in ethanol at room temperature for 24 hours, and with aniline in refluxing ethanol [where no reaction took place at room temperature], ring opening took place giving 2-benzoylamino-5-bromo-N-substituted benzamides (2 & 3), respectively. Morpholine as an example of secondary amines reacted similarly with (1) to give the corresponding benzamide derivative (4) (scheme).

The structures of (2-4) were infered from: i) Analytical data ii) Their infrared spectra show sharp bands at 3250 - 3280 cm^{-1} characteristic of NH stretching frequencies in addition to strong absorptions at 1630 - 1670 cm^{-1} characteristic of carbonyl stretching frequencies of amides (cf. table).

In all above reactions it was not possible to isolate any amidine salt indicating that there is no possibility of nucleophilic attack by the amine at position 2-.

The reaction of hydrazine hydrate with ethanolic solution of (1) at room temperature yielded 2-benzoylamino - 5-bromobenzhydrazide (5). However, when the reaction was carried out in refluxing glacial acetic acid containing catalytic amount of fused sodium acetate, 3-acetylamino-6-bromo-2-phenylquinazolin-4-one (6) was formed. The latter compound was also formed via cyclisation of the hydrazide (5) using acetic anhydride under reflux for 1 hour (cf. scheme). However, when the hydrazide (5) was heated with acetic anhydride for 5 hours, extrusion of hydrazine molecule took place yielding 6-bromo-2-phenyl-3,1-benzoxazin-4-one (1) as indicated by m.p. and m.m.p. experiments and also by superimposable - infrared spectra (νCO 1750 cm^{-1}).

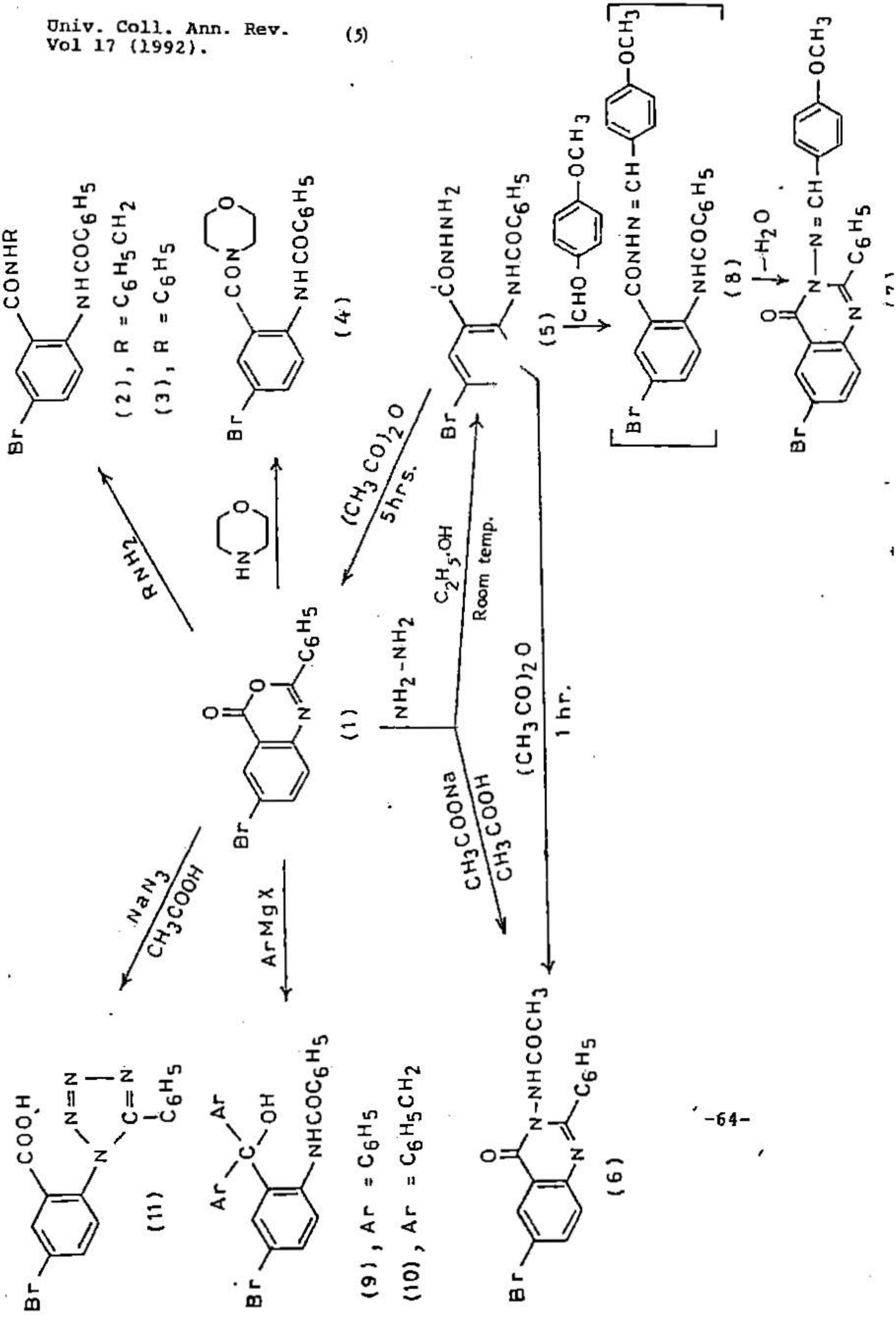
The structures of (5 & 6) were confirmed, other than from analytical data, from a study of their infrared spectra. Thus the infrared spectrum of (5) shows the bands characteristic of ν HN and νCO of amides while that of (6) shows the stretching frequencies of NH and carbonyl groups of both quinazolinones and amides (cf. table).

The reaction of the hydrazide (5) with p-methoxybenzaldehyde was conducted in refluxing glacial acetic acid containing fused sodium acetate to give 6-bromo-3-p-methoxybenzylideneamino-2-phenylquinazolin-4-one (7). The reaction evidently involved the intermediate formation of 2-benzoylamino-5-bromo-N-p-methoxybenzylidenebenzhydrazide (8). The possibility that the cyclisation process preceeded condensation with p-methoxybenzaldehyde was overailed since as mentioned above cyclisation under these condition yeilds (6).

The structure of (7) was substantiated from: i) Analytical data. (ii) Its infrared spectrum shows the carbonyl stretching frequency of quinazolin-4-one while it lacks any significant absorption in the 3 μ region (cf. table).

When (1) was allowed to react with phenylmagnesium bromide or with benzylmagnesium chloride, the carbinols (9 & 10), respectively were produced. The structure of these carbinols was established, beside analytical data, from their infrared spectra which show two bands in the 3 μ region characteristic of OH and NH stretching frequencies in addition to the carbonyl stretching frequency of anilides (cf. table).

The present investigation was extended to involve the action of hydrazoic acid [sodium azide and acetic acid] on 6-bromo-2-phenyl-3,1-benzoxazin-4-one (1) whereupon, the tetrazolyl acid derivative (11) was obtained. The structure of (11) was confirmed from: i) Elemental analysis. ii) It dissolves easily in aqueous sodium carbonate and reprecipitates by the addition of a mineral acid. iii) Its infrared spectrum shows a broad band in the 3μ region characteristic of OH stretching frequency of carboxylic acids in addition to the carbonyl stretching frequency (cf. table).


(1)
RNH2
(2), R = C6H5CH2
(3), R = C6H5
CONHR
NHCOC6H5
(4)
(CH3CO)2O 5hrs.
NH2-NH2
C2H5OH Room temp.
(5)
CONHNH2
CHO
OCH3
CONHN = CH
(8)
-H2O
(7)
N-N = CH
(CH3CO)2O 1 hr.
CH3COONa CH3COOH
(6)
N-NHCOCH3
ArMgX
(9), Ar = C6H5
(10), Ar = C6H5CH2
NaN3 CH3COOH
(11)
COOH
Br

Experimental

All melting points are uncorrected. Elemental analyses were carried out at the Microanalytical Unit, Cairo University. I.R. spectra in KBr were recorded on a PYE - Unicam SP 1200 spectrophotometer.

Reaction of 6-bromo-2-phenyl-3,1-benzoxazin-4-one (1) with amines:

The solution of (1, 0.01 mole) in ethanol (20 ml) was treated with the amine (0.01 mole) and the reaction mixture was left overnight at room temperature with occasional shaking. The solid formed was filtered off and crystallised from benzene - light petroleum (b.p. 90-100°C) mixture to give 2-benzoylamino-5-bromo-N-substituted benzamides (2 & 4), as colourless crystals.

In the case of the reaction of (1) with aniline, the reaction mixture was heated under reflux for 10 hours. The product was crystallised from benzene - light petroleum (b.p. 90-100°C) mixture to give 2-benzoylamino-5-bromo-N-phenylbenzamide (3), as colourless crystals (cf. table).

Reaction of (1) with hydrazine hydrate :

A- Reaction in elthanol :

A solution of (1, 0.01 mole) in ethanol (20 ml) was treated with hydrazine hydrate (1 ml) and the reaction mixture was left overnight at room temperature with occasional shaking. The solid formed was filtered off and crystallised from benzene - ethanol mixture to give 2-benzoylamino-5-bromobenzhydrazide (5), as colourless crystals (cf. table).

B- Reaction in glacial acetic acid

A mixture of (1, 0.01 mole), hydrazine hydrate (1 ml) and fused sodium acetate (0.2 gm) in glacial acetic acid (20 ml) was heated under reflux for 8 hours, then poured into cold water. The solid formed was filtered off and crystallised from benzene to give 3-acetylamino-6-bromo-2-phenylquinazolin-4-one (6), as colourless crystals (cf. table).

Action of acetic anhydride on 2-benzoylamino-5-bromobenzhydrazide (5):

(i) Formation of 3-acetylamino-6-bromo-2-phenylquinazolin-4-one (6)

A mixture of (5, 1 gm) and acetic anhydride (15 ml) was heated under reflux for 1 hour. The reaction mixture was poured into cold water and the solid formed was filtered off and crystallised from benzene to give 3-acetylamino-6-bromo-2-phenylquinazolin-4-one (6), as colourless crystals (cf. table). The product showed no depression when admixed with the product of the reaction of (1) with hydrazine hydrate in glacial acetic acid.

(ii) Formation of 6-bromo-2-phenyl-3,1-benzoxazin-4-one (1)

The reaction was carried out as described in the above experiment and extending the time of reflux for 5 hours. The product formed was crystallised from benzene to give 6-bromo-2-phenyl-3,1-benzoxazin-4-one (1), as pale yellow crystals, m.p. and m.m.p. 194°C, yield 30 %.

Reaction of 2-benzoylamino-5-bromobenzhydrazide (5) with p-methoxybenzaldehyde in glacial acetic acid

A mixture of (5, 0.01 mole), p-methoxybenzaldehyde (0.01 mole) and fused sodium acetate (0.2 gm) in glacial acetic acid (20 ml) was heated under reflux for 8 hours, then poured into cold water. The solid formed was filtered off and crystallised from benzene to give 6-bromo-3-p-methoxybenzylideneamino-2-phenylquinazolin-4-one (7), as colourless crystals (cf. table).

Reaction of Grignard Reagents with 6-bromo-2-phenyl-3,1-benzoxazin-4-one (1)

A solution of the appropriate Grignard reagents (0.03 mole) in dry ether (50 ml) was added to a solution of 6-bromo-2-phenyl-3,1-benzoxazin-4-one (0.01 mole) in dry benzene (60 ml) with occasional shaking. The reaction mixture was heated under reflux on a boiling water-bath for 5 hours and left overnight. The reaction mixture was then hydrolysed by shaking with a saturated solution of ammonium chloride. The benzene - ether layer was washed several times with cold water, separated, dried over anhydrous sodium sulphate, concentrated under reduced pressure and left to cool. The reaction product was then treated as described in individual experiments.

A- Reaction of (1) with phenylmagnesium bromide

The colourless solid formed was crystallised from benzene - ethanol mixture to give 2-benzoylamino-5-bromophenyl diphenyl carbinol (9), as colourless crystals (cf. table).

B- Reaction of (1) with benzylmagnesium chloride

The reaction was carried out as described before. Evaporation of the organic layer gave a colourless solid which was crystallised from benzene to give 2-benzoylamino-5-bromophenyl dibenzyl carbinol (10), as colourless crystals (cf. table).

Action of sodium azide and glacial acetic acid on 6-bromo-2-phenyl-3,1-benzoxazin-4-one (I)

A mixture of (I, 0.01 mole) in glacial acetic acid (5 ml) was treated with a solution of sodium azide (0.015 mole) in the least amount of water and the mixture was heated on a boiling water-bath for 5 hours. The mixture was cooled and then diluted with water. The solid separated was filtered off and crystallised from benzene - ethanol mixture to give the tetrazolyl acid derivative (11), as colourless crystals (cf. table).

Physical data of compounds 2 - 11

Compound	M.p. (°C)	Yield (%)	Molecular formula	Analysis Found/Calcd (%)				I.R.(cm^{-1})	
				C	H	N	Br	$\nu_{NH,OH}$	ν_{CO}
2	168-170	65	$C_{21}H_{17}N_2O_2Br$			6.79	19.40	3280	1630
						6.84	19.55		1670
3	205-207	60	$C_{20}H_{15}N_2O_2Br$			7.14	19.80	3250	1640
						7.08	20.25		1655
4	175-177	70	$C_{18}H_{17}N_2O_3Br$			7.21	20.40	3260	1630
						7.19	20.56		1665
5	177-179	85	$C_{14}H_{12}N_3O_2Br$			12.71	23.80	3290	1620
						12.57	23.95		1670
6	108-110	70	$C_{16}H_{12}N_3O_2Br$	54.00	3.60		22.00	3250	1670
				53.63	3.35		22.34		1700
7	209-211	68	$C_{22}H_{16}N_3O_2Br$	60.26	3.09	9.93	18.30		1690
				60.82	3.68	9.67	18.43		
9	215-217	85	$C_{26}H_{20}NO_2Br$			3.14	17.30	3300	1660
						3.05	17.46	3400	
10	178-180	70	$C_{28}H_{24}NO_2Br$			3.01	16.50	3280	1650
						2.88	16.46	3370	
11	173-175	50	$C_{14}H_9N_4O_2Br$			15.38	23.40		
						16.23	23.18	3180-3440	1720

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ملخص البحث

يناقش هذا البحث تفاعل ٦ ـ برومو ـ ٢ ـ فينيل ـ ٣،١ ـ بنزواكزازين ـ ٤ ـ أون (١) مع بعض الامينات مثل البنزيل أمين ، الانيلين أو المورفولين مع فتح الحلقة لكي يعطى مشتقات البنزاميد المقابلة (٢ ـ ٤) . عند تفاعل (١) مع هيدرات الهيدرازين فى الكحول فانه يعطى مشتق البنزهيدرازيد (٥) بينما يتفاعل فى وجود حامض الخليك الثلجى وكمية قليلة من خلات الصوديوم معطيا ٣ ـ أسيتيل أمينو ـ ٦ ـ برومو ـ ٢ ـ فينيل كونيازولين ـ ٤ ـ أون (٦) وهذا المركب الاخير يمكن الحصول عليه من تسخين الهيدرازيد (٥) مع أنهيدريد حامض الخليك لمدة ساعة واحدة كما تفاعل الهيدرازيد (٥) مع بارا ميثوكس بنزالدهيد ليعطى ٦ ـ برومو ـ ٣ ـ بارا ميثوكس بنزايليدين أمينو ـ ٢ ـ فينيل كونيازولين ـ ٤ ـ أون (٧). أما تفاعل (١) مع بروميد فينيل الماغنسيوم وكلوريد بنزيل المغنسيوم فقد أعطى الكربينولات المقابلة (٩ ، ١٠). وقد امتد هذا البحث ليتضمن الحصول على مشتق حامض التترازوليل من تفاعل (١) مع حمض الهيدرازويك