Reactions of 6,8-dibromo-2-(3,5-dinitrophenyl)-4H-Benz[4]oxazin-4-one with Nitrogen and Carbon Nucleophiles

M.E. Shaban, A.M. Yousef, N.K. Elaaser and A.K. El-Ziaty

Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, 11566, Egypt

Abstract: The hitherto unknown 6,8-dibromo-2-(3,5-dinitrophenyl)-4H-benzo[d][1,3]oxazin-4-one was constructed and its proclivity with some nitrogen and carbon nucleophiles was studied. Compound 1 was utilized as scaffold for novel quinazolinone derivatives 8-10 and 12. Novel heterocycles 11,13-15 were also constructed from benzoxazinone 1. All the newly synthesized compounds were characterized by physical and chemical tools (IR, 1H NMR and MASS spectra).

Key words: 4H-benzo[d][1,3]oxazin-4-one · Quinazoline-4(3H)-one · Benzo[d]imidazol · Quinoline-3-carboxylic acid and quinoline-3-carbonitrile

INTRODUCTION

Benzoxazines and their derivatives have been received great attention, some of them proved to be of special importance in medicine as antifungal, anticoagulant, antispasmodic and antiallergic agents [1]. 2-(4-Toluenesulphonyl)oxy phenyl 3,1-benzoxazine-4-one was prepared and reacted with some nitrogen nucleophiles, the antimicrobial antifungal activity of all the products were evaluated [2]. A series of 2,8-disubstituted benzoxazinones were synthesized and subjected to anti-platelet aggregation, inhibition of superoxide anion generation and inhibition of neutrophil elastase release assays [3].

One-pot montmorillonite K-10 clay-supported three-component reactions of substituted salicylaldehydes, ribosyl/deoxyribosyluracils and ammonium acetate expeditiously yield the novel N-nucleosides, 4-amino-3,4-dihydro-3-(b-D-ribo- or b-D-20-deoxyribofuranosyl)-2H-benz[e]-1,3-oxazin-2-ones; via cycloisomerisation of an aldimine intermediate under solvent-free microwave irradiation conditions [4]. A series of 2-substituted benzoxazinones were synthesized and subjected to anti-human coronavirus and ICAM-1 expression inhibition assays [5].

A new method has been designed to prepare the known benzoxazinone derivative 2-(N-phthaloylmethyl)-4H-3,1-benzoxazin-4-one. The acyl chloride derivative N-phthaloylglycine reacts with anthranilic acid in chloroform; in the presence of triethylamine, to give an intermediate that is then reacted with cyanuric chloride, used as a cyclization agent; to produce the benzoxazinone derivative [6]. A new series of 6-iodo-2-undecylquinazolin-4(3H)-ones were prepared via reaction of 6-iodo-2-undecyl-4H-benzoxazin-4-one with nitrogen nucleophiles, namely, primary amines, 4-amino antipyrine, hydrazine hydrate, diamines, ethanol amine and/or hydrazide derivatives and screened for their antitumor activity in vitro against a panel of three human tumor cell lines namely; hepatocellular carcinoma (liver) HepG2; colon cancer HCT-116; and mammary gland breast MCF-7 [7].

6,8-Dibromo-(4H)-3,1-benzoxazinone was synthesized and allowed to react with some nitrogen nucleophiles [8]. A series of benzoxazinones were synthesized via reaction of anthranilic acid with various substituted benzoyl chlorides in the presence of triethylamine in chloroform, showed a good inhibition of α-chymotrypsin with IC50 ± SEM values between 6.5 and 341.1 µM [9].

In continuation of our efforts towards construct heterocyclic compounds and evaluate their pharmaceutical importance [10-28], the present work deals with synthesis of new benzoxazinone derivative bearing a bulky moiety at position 2, in order to study the stability and reactivity of benzoxazinone nucleus toward some different nucleophilic reagents.

Corresponding Author: M.E. Shaban, Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, 11566, Egypt.
RESULTS AND DISCUSSION

The hitherto unknown 6,8-dibromo-2-(3,5-dinitrophenyl)-2H-benzo[d][1,3] oxazin-4-one 1 was constructed in situ from the reaction of 3,5 dibromoanthranilic acid and 3,5 dinitrobenzoyl chloride in the presence of dry pyridine as a solvent. (Scheme 1).

The structure assignment of compound 1 was substantiated from its correct elemental analysis (c.f. experimental section). I.R of compound 1 showed absorption bands at $\nu$ 1766 cm$^{-1}$ (lactonic C=O), $\nu$ 1621 cm$^{-1}$ (C=N), and showed a signal at 1671 cm$^{-1}$ for the carbonyl groups. Hydroxylamine hydrochloride, hydrazine hydrate and semicarbazide hydrochloride were used as nitrogen and carbon nucleophiles, where the reaction of compound 1 with hydroxylamine hydrochloride, hydrazine hydrate and semicarbazide hydrochloride in n-butanol as a solvent. The structure assignment of compounds 8-10 was substantiated from their I.R spectra which exhibited no signal corresponding to the lactonic carbonyl at $\nu$ 1766 cm$^{-1}$ and showed a signal at $\nu$ 1691-1660 cm$^{-1}$ for the lactam carbonyl of quinazolines.

As a chemical evidence of the structures of compound 2-10, Compound 3 was underwent ring closure on boiling in n-butanol to compound 9 (Scheme 2).

On the other hand o-phenylene diamine reacted with benzoxazinone 1 in boiling n-butanol afforded the N-(2-(1H-benzo[d]imidazol-2-yl)-4,6-dibromophenyl)-3,5-dinitrobenzamide 11 which structure was proved from the I.R spectra which displayed a strong absorption band at $\nu$ 1662 cm$^{-1}$ (C=O), 1625 cm$^{-1}$ (C=N) and 3230 cm$^{-1}$ (NH), the mass spectrum confirms the structure of compound 11, showed the correct molecular ion peak at m/z = 559 (14.6%) together with [M+2] and [M+4] peaks at m/z = 561 (27.6%), 563 (15%) respectively and the base peak at m/z = 75 (100%).

Fusion of benzoxazinone 1 with formamide and/or ammonium acetate yielded 6,8-dibromo-2-(3,5-dinitrophenyl)quinazolin-4(3H)-one 12. The structure of quinazolin-4-one derivative 12 was elucidated from the following data, IR ($\nu$ cm$^{-1}$): 3174, (NH(OH)),1671 cm$^{-1}$ (C=O), 1608 cm$^{-1}$ (C=N). $^1$H-NMR (DMSO-d$_6$) of t $\delta$ ppm. 10.01 (s,1H, NH), disappeared by D$_2$O 9.02-8.81 (m, 2H$_{\text{arom}}$), 8.75-8.69 (m, 3H$_{\text{arom}}$).

Ring opening of compound 1 with hydrazoic acid gave 3,5-dibromo-2-(5-(3,5-dinitrophenyl)-1H-tetrazol-1-yl)benzoic acid 13.
By studying the reaction of benzoxazinone 1 with active methylene compounds as carbon nucleophiles, compound 1 was allowed to react with diethyl malonate and/or ethyl cyanoacetate in the presence of dry pyridine as a catalyst base the reaction occurred via heterocyclic ring opening at position -4- by carbanion of active methyleneto form firstly an open adduct as an intermediate which cyclized to form afforded 6,8-dibromo-2-(3,5-dinitrophenyl)-4-oxo-3,4-dihydroquinoline-3-carboxylic acid, 14 and 6,8-dibromo-2-(3,5-dinitrophenyl)-4-oxo-3,4-dihydroquinoline-3-carbonitrile 15 (Scheme 3). The structure assignment of compounds 14 and 15 were substantiated from its correct elemental and spectral data (I.R, ¹H NMR and MASS).
Scheme 4: The mechanism of the reaction on benzoxazinone with active methylene compounds

The mechanism of formation of 14 and 15 was discussed in the following scheme (scheme 4).

**Experimental:** Melting points are uncorrected and were measured by an electric melting point apparatus (G-K). The IR spectra were recorded on a Pye-Unicam SP1200 spectrophotometer using KBr Wafer technique. The °H-NMR spectra were determined on a Varian GEMINI 200 MHz NMR spectrophotometer using CDCl₃ or DMSO-d₆ as solvent and TMS as an internal standard. All chemical shifts are in ppm downfield from TMS. The elemental analysis were carried out in faculty of Science, Ain Shams University. MS were recorded on Shimadzu GC-MS QP1000EX instrument in micro analytical lab, Cairo University. The monitoring of the progress of all reactions and homogeneity of the synthesized compound was carried out by TLC.

6,8-dibromo-2-(3,5-dinitrophenyl)-4H-benzo[d][1,3]oxazin-4-one (1): To a solution of 3,5 dibromoanthranilic acid (0.01mol) in dry pyridine (50ml), 3,5 dinitrobenzoyl chloride (0.01mol) in dry diethyl ether (30ml) was added dropwise with stirring. The reaction mixture was heated on water bath for 2 hours, poured on ice cold water and HCl. The solid separated was filtered off dried and recrystallized from benzene/ethano mixture to give I as pale yellow crystals, m.p: 238-240°C.Yield (80%). Anal. Calcd.: for C₁₅H₇Br₂N₂O₆ (471): C, 35.66; H, 1.06; N, 8.91 Found: C, 35.26; H, 1.02; N, 8.73; IR (υ cm⁻¹): 1766cm⁻¹ (lactonic C=O), 1612 cm⁻¹ (C=N). MS m/z (%), m/z= 469 (28.6%) together with [M+2] and [M+4] peaks at m/z= 471 (54.6%), 473 (30%) respectively and the base peak at m/z= 75 (100%). °H-NMR (DMSO-d₆) of t δ ppm. 9.10-9.05 (m, 2H), 8.55-8.29 (m, 3H).

**General Procedure For The Synthesis of Compounds**

2-7: A mixture of benzoxazinone 1 (0.01mol) and primary amines and/or secondary amines namely benzyl amine, hydrazine, benzoyl hydrazine, guanidine hydrochloride, pipridine and morpholine (0.01mol) in ethanol (50ml) was refluxed for four hours. The solid obtained was filtered off dried and recrystallized from proper solvent.

N-benzyl-3,5-dibromo-2-(3,5-dinitrobenzamido) benzamid (2): Recrystallized from dioxane. m.p: 260-262°C.Yield (68%). Anal. Calcd.: for C₂₇H₁₈Br₂N₂O₆ (578): C, 43.60; H, 2.42; N, 9.68. Found: C, 43.35; H, 2.22; N, 9.56; IR (υ cm⁻¹): 3426 and 3419 (NH/OH),1656 cm⁻¹ (C=O), 1630 cm⁻¹ (C=N). MS m/z (%) m/z= 578 (18.6%) together with [M+2] and [M+4] peaks at m/z= 581 (34.6%), 583 (30%) respectively and the base peak at m/z= 75 (100%). °H-NMR (DMSO-d₆) of t δ ppm. 11.02 (s,1H, NH), 10.76 (S,1H, NH ), 9.10-9.05
General Procedure For The Synthesis of Compounds

8-10: A mixture of primary amines namely hydroxyl amine hydrochloride, hydrazine hydrate and semicarbazide hydrochloride (0.01mol) in n-butanol (50ml) was refluxed for four hours the solid obtained after evaporating the solvent was filtered off, dried and recrystallized from suitable solvent.

N-(2,4-dibromo-6-(piperidine-1-carbonyl)phenyl)-3,5-dinitrobenzamide (6): Recrystallized from dimethylformamide. m.p: 200-242°C. Yield (72%). Anal. Calcd.: for C_{12}H_{10}Br_{12}N_{2}O_{6} (556): C, 39.68; H, 2.87; N, 10.07. Found: C, 39.68; H, 2.76; N, 9.92; IR (ν cm⁻¹): 3181, 3442 (NH), 1677 cm⁻¹ (C=O), 1608 cm⁻¹ (C=N). 1H-NMR (DMSO-d₆) of t δ ppm. 10.22 (s, 1H, NH), disappeared by D₂O. 8.75-8.69 (m, 3H, arom), 4.92 (m, 10H, CH₂). MS m/z (%) m/z=556 [M+2] (30.6%), together with [M+1] and [M+3] peaks at m/z= 558 (60.6%), 562 (30%) respectively, m/z=232 (4.8%), m/z=234 (12.8%), m/z=236 (7.8%), m/z=193 (13.8%) and the base peak with m/z= 74 (100%).

N-(2,4-dibromo-6-(morpholine-4-carbonyl)phenyl)-3,5-dinitrobenzamide (7): Recrystallized from dimethylformamide. m.p: 240-242°C. Yield (45%). Anal. Calcd.: for C_{13}H_{12}Br_{12}N_{2}O_{6} (558): C, 38.71; H, 2.51; N, 10.03. Found: C, 38.86; H, 2.34; N, 9.98; IR (ν cm⁻¹): 3122, 3448 (NH), 1679 cm⁻¹ (C=O), 1614 cm⁻¹ (C=N). 1H-NMR (DMSO-d₆) of t δ ppm. 9.92 (s, 1H, NH), disappeared by D₂O. 8.82-8.78 (m, 2H, arom), 8.71-8.62 (m, 3H, arom) and 4.62 (m, 8H, CH₂).
m.p: 280-282°C. Yield (78%). Anal. Calcd.: for C_{16}H_{15}BrN_{2}O_{2} (561): C, 42.78; H, 1.96; N, 12.47. Found: C, 42.63; H, 1.88; N, 12.32. IR (υ cm⁻¹): 3477, (OH), 1690 cm⁻¹. H-NMR (DMSO-d₆) of t δ ppm. 10.92 (s, 1H, NH), 8.92-8.81 (2H, arom), 8.75-8.69 (m, 3H, arom) and 7.92 (m, 4H, arom), 3.16 (s, 1H, NH), disappeared by D₂O.

6,8-dibromo-2-(3,5-dinitrophenyl)quinazolin-4(3H)-one (12): A mixture of benzoazinone 1 (0.01mol) and 20 ml formamide and/or (0.01) mol amm. Acetate was refluxed on oil bath at 220°C for three hours. the reaction mixture was poured onto cold water and the solid separated was filtered off, dried and recrystallized from dimethylformamide, to give 12 as pale yellow crystals. m.p: over 300°C. Yield (78%). Anal. Calcd.: for C₁₆H₁₅BrN₂O₂ (470): C, 35.74; H, 1.27; N, 11.91. Found: C, 34.23; H, 1.19; N, 11.78; IR (υ cm⁻¹): 3174, (NH/OH), 3452, (OH), 1690 cm⁻¹. H-NMR (DMSO-d₆) of t δ ppm. 10.02 (s, 1H, NH), disappeared by D₂O, 9.02-8.81 (m, 2H, arom), 8.75-8.69 (m, 3H, arom) and 7.92 (m, 4H, arom). 6,8-dibromo-2-(3,5-dinitrophenyl)-4-oxo-3,4-dihydroquinoline-3-carboxylic acid (14): m.p: 210-212°C. Yield (40%). Anal. Calcd.: for C_{16}H_{15}BrN_{2}O_{3} (513): C, 37.42; H, 1.36; N, 8.18. Found: C, 37.23 H, 1.29; N, 8.02; IR (υ cm⁻¹): 3452, (OH), 1690 cm⁻¹ (C=O), 1604 cm⁻¹ (C=N). H-NMR (DMSO-d₆) of t δ ppm. 10.92 (s, 1H, COOH), 8.92-8.81 (m, 2H, arom), 8.75-8.69 (m, 3H, arom) and 5.16 (s, 1H, CH). 6,8-dibromo-2-(3,5-dinitrophenyl)-4-oxo-3,4-dihydroquinoline-3-carbonitrile (15): m.p: 220-222°C. Yield (38%). Anal. Calcd.: for C₁₆H₁₅BrN₂O₂ (494): C, 38.86; H, 1.21; N, 11.33. Found: C, 38.76; H, 1.12; N, 11.20; IR (υ cm⁻¹): 2212, (CN),1680 cm⁻¹ (C=O), 1604 cm⁻¹ (C=N). H-NMR (DMSO-d₆) of t δ ppm. 8.92-8.81 (m, 2H, arom), 8.75-8.69 (m, 3H, arom). 4.96 (s, 1H, CH).

CONCLUSION

During the current investigation, we synthesized a new building block; namely 6,8-dibromo-2-(3,5-dinitrophenyl)-4H-benzo[d][1,3]oxazin-4-one and its proclivity with nitrogen and carbon nucleophiles was studied. From that compound, a series of different quinazoline and quinoline derivatives were synthesized and their structural and spectral data were elucidated.

ACKNOWLEDGMENTS

The authors are appreciative to Chemistry Department, Faculty of Science, Ain Shams University where the experimental part carried out in its laboratories and micro analytical lab, Cairo University where the spectral analysis was carried out.

REFERENCES


General Procedure For The Reaction of Benzoazinone With Active Methylene Compounds: A mixture of benzoazinone 1 (0.01mol) and active methylene compounds namely diethyl malonate and/or ethyl cyanoacetate (0.01mol) in dry pyridine (30ml) was refluxed for ten hours. The reaction mixture was poured onto crushed ice and acidified with 10% cold HCl (20ml). The formed precipitate was filtered off, washed with water, dried and recrystallized from benzene/ethanol mixture to give 14 and 15 as yellow crystals.