Synthesis of 6-iodo / bromo- 3-amino-2-methylquinazolin-4 (3*H*)-ones by direct halogenation and their Schiff base derivatives

Mudassar A. Sayyed, Shyam S. Mokle, and Yeshwant B.Vibhute*

P.G. Department of Chemistry, Yeshwant Mahavidyalaya, Nanded-431602 (MS) India
E-mail: drybvibhute@yahoo.com

Abstract
Treatment of 3-amino-2-methylquinazolin-4(3*H*)-one with iodine monochloride or bromine in acetic acid affords the corresponding 6-iodo / bromo 3-amino-2-methylquinazolin-4 (3*H*) -ones in high yields. The notable advantages of this protocol are, no need of catalyst, mild conditions, simple operation and short reaction times with high yields. New potentially active Schiff bases are prepared by condensing these 6-iodo / bromo 3-amino-2-methylquinazolin-4 (3*H*) -ones with different substituted aryl aldehydes. The bioactivity of the synthesized Schiff bases is studied.

Keywords: 6-iodo / bromo 3-amino-2-methylquinazolin-4 (3*H*) –ones, Schiff bases, antibacterial activity

Introduction

In recent years there has been an increased interest in the chemistry of quinazoline-4 (3*H*)-ones because of their biological significance. Many of them show antifungal[1], antibacterial[2], anticancer[3], antiinflammatory[4], anticonvulsant[5], immunotropic[6], hypolipidemic[7], antitumor[8], antiulcer[9], analgesic[10], and antiproliferative[11] activities as well as inhibitory effects for thymidylate synthase[12], and poly(ADP-ribose) polymerase (PARP)[13]. The remarkable synthetic properties of quinazolinone derivatives have ensured long-standing studies of their utilization in organic synthesis. However, the literature methods[14,15] for synthesis of halosubstituted quinazolinone derivatives have required haloanthranilic acids and this method suffers from serious drawbacks, which include mixture formation, long reaction times, low yields, tedious work up procedures. Therefore, there is need for the development of an improved protocol.

Results and Discussion

The starting compound 3-amino-2-methylquinazolin-4(3*H*)-one (**2**) was prepared according to a literature method[16]. We report herein the use of iodine monochloride and bromine in acetic acid for direct iodination and bromination of 3-amino-2-methylquinazolin-4 (3*H*) -one leading to 6-iodo / bromo 3-amino-2-methylquinazolin-4 (3*H*) -ones **(Scheme 1)**.

Further, we have condensed 6-iodo / bromo 3-amino-2-methylquinazolin-4 (3*H*)-ones (**3**, **4**) with aromatic aldehydes in the presence of trace amounts of acetic acid to yield Schiff bases **(Scheme 1)**. The structures of the compounds were confirmed by spectral and analytical data or by comparison of their melting points with samples prepared by known methods [14,15].

Biological Activity

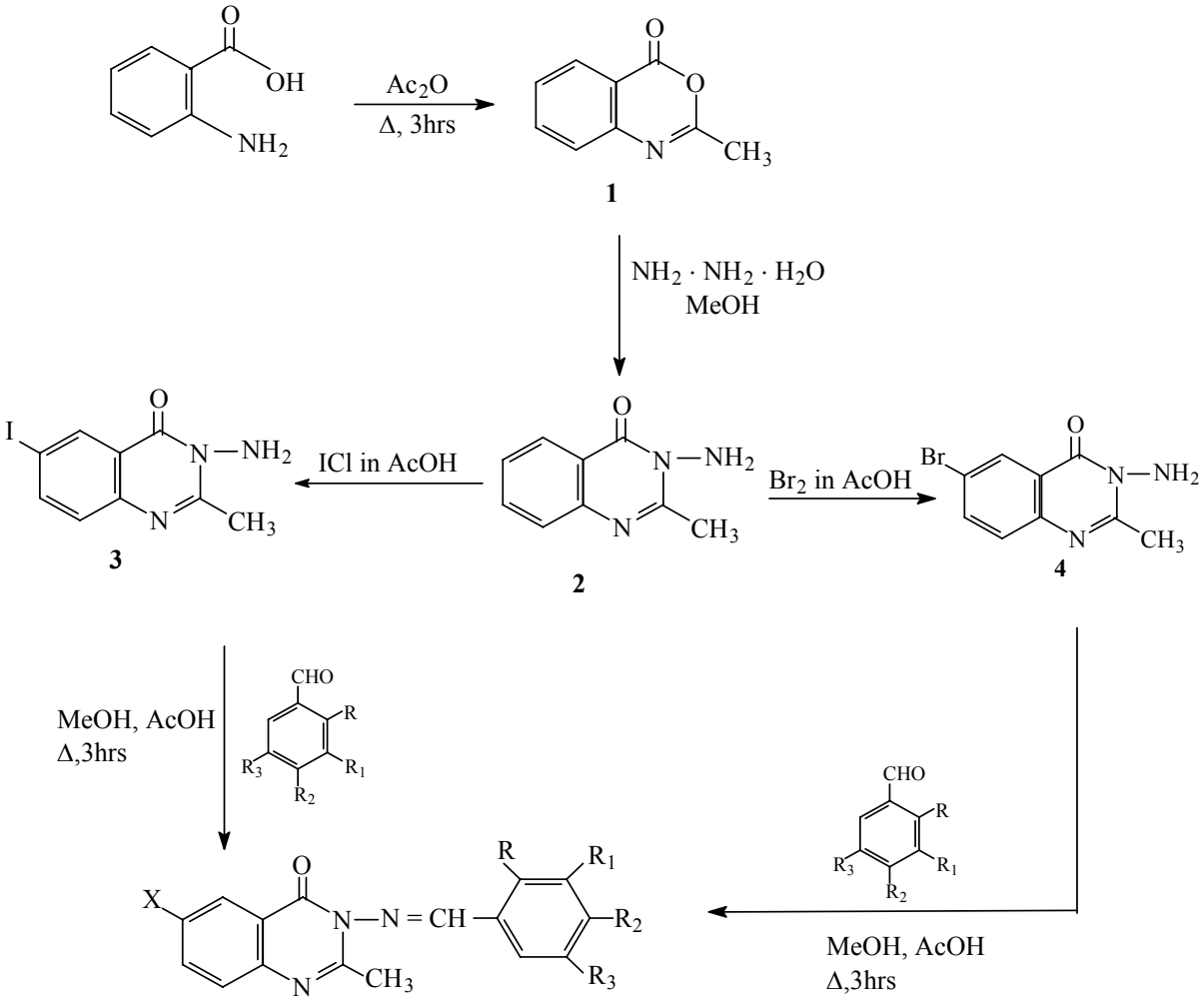
Most of the newly synthesized compounds were tested for their antibacterial activity in *vitro* against bacterial strains such as *Escherichia coli* and *Staphylococcus aureus* employing the nutrient agar disc diffusion method[17] at 100 ppm concentration in DMSO. The results showed that all the compounds exhibited a marked degree of activity against bacteria in comparison to *Tetracycline*, which was taken as a standard drug. The results showed the degree of inhibition varied with the tested compounds. The zones of inhibition of synthesized compounds in mms for *E .coli* and *S. aureus* are: **5a** (08,09), **5b** (06,12), **5c** (14,13), **5d** (15,12), **5e** (20,19), **5f** (19,17), **5g** (09,11), **5h** (12,14), **5i** (27,24) and **5j** (24,20), *Tetracycline* (16,14), respectively.

Experimental Part

All melting points were taken in open capillaries and are uncorrected. The IR spectra in KBr were recorded on a Perkin Elmer 157 spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR spectra on a Bruker WM 400MHz FT-NMR instrument using $CDCl_3$ or DMSO-d_6 as a reference (chemical shifts in δ ppm). The homogeneity and purity of the compounds were ascertained by TLC on silica gel G plates. The spots were developed in an iodine chamber.

Synthesis of 6-iodo-3-amino-2-methylquinazolin-4 (3*H*)-one (3). To a solution of 3-amino-2-methylquinazolin-4 (3*H*)-one (1.75g, 0.01m) in acetic acid (15ml) was added iodine monochloride (0.01m, 20% ICl in acetic acid, 8ml). The reaction mixture was kept overnight at room temperature then poured on ice-cold water. The solid that separated was filtered, dried and recrystallized from ethyl alcohol to give the title compound.

Yield: 75%; m.p. 203^{0}C (Literature m.p. 203^{0}C)[14], Found (%) I, 42.46. Calc. For $C_9H_8N_3OI$ (%) I, 42.19; IR (cm^{-1}) 3446 (NH of NH_2), 1689 (N-C=O quinazolinone), 1602 (C=N).



5 a-j

5 a = X = I, R = H, R_1 = Br, R_2 = OH, R_3 = OCH_3
5 b = X = I, R = H, R_1 = I, R_2 = OH, R_3 = OCH_3
5 c = X = I, R = OH, R_1 = I, R_2 = H, R_3 = I
5 d = X = I, R = OH, R_1 = Br, R_2 = H, R_3 = Br
5 e = X = I, R = OH, R_1 = Cl, R_2 = H, R_3 = Cl
5 f = X = Br, R = H, R_1 = Br, R_2 = OH, R_3 = OCH_3
5 g = X = Br, R = H, R_1 = I, R_2 = OH, R_3 = OCH_3
5 h = X = Br, R = OH, R_1 = I, R_2 = H, R_3 = I
5 i = X = Br, R = OH, R_1 = Br, R_2 = H, R_3 = Br
5 j = X = Br, R = OH, R_1 = Cl, R_2 = H, R_3 = Cl

Scheme 1

Synthesis of 6-bromo- 3-amino-2-methylquinazolin-4 (3*H*)-one (4). To a solution of 3-amino-2-methylquinazolin-4 (3*H*)-one (**2**) (1.75g, 0.01m) in acetic acid (15ml) was added bromine in acetic acid (0.01m, 20% bromine in acetic acid, 8ml). The reaction mixture was kept overnight at room temperature then poured on ice-cold water. The solid that separated was filtered, dried and recrystallized from ethyl alcohol to give the title compound. Yield: 55%; m.p. 196^{0}C (Literature m.p. 197^{0}C)[14], Found (%) Br, 31.12. Calc. For $C_9H_8N_3OBr$ (%), Br: 31.37; IR (cm^{-1}): 3448 (NH of NH_2), 1686 (N – C = O quinazolinone), 1605 (C = N).

General procedure for the preparation of Schiff bases 5a-j. To a solution of halohydroxy substituted benzaldehyde (0.01mol) in methanol (15 ml), was added the appropriate 6-halosubstituted-3-amino-2-methylquinazolin-4(3H)-one (0.01 mol) and a few drops of acetic acid. The reaction mixture was refluxed for 3h, cooled, poured into ice-cold water, and the separated solid filtered, dried and recrystallized from ethanol to afford **5a-5j**.

3-(3-Bromo-4-hydroxy-5-methoxybenzalamino)-3-amino-6-iodo-2-methyl-quinazolin-4 (3H)-one (5a). Yield 75%, mp 232°C, IR (cm^{-1}) 3269, 1669, 1598, 1500. ^{1}H NMR (DMSO-d_6) δ: 2.55 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.5-8.2 (m, 5H, Ar-H), 8.82 (s, 1H, =CH). 10.52 (s, 1H, OH). Anal. Calcd. for $C_{17}H_{13}N_3O_3IBr$: N, 8.17, % of I & Br, 40.27. Found : N, 7.78, % of I & Br , 39.87.

3-(3-Iodo-4-hydroxy-5-methoxybenzalamino)-6-iodo-3-amino-2-methylquinazolin-4 (3H)-one (5b). Yield 68%, mp 245°C, IR (cm^{-1}) 3220, 1670, 1595, 1500. ^{1}H NMR (DMSO-d_6) δ: 2.68 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 7.2-8.6 (m, 5H, Ar-H), 8.7 (s, 1H, =CH). 10.52 (s, 1H, OH). Anal. Calcd. for $C_{17}H_{13}N_3O_3I_2$: N, 7.48,I, 45.27. Found : N, 7.25, I, 45.87.

3-(2-Hydroxy-3,5-diiodobenzalamino)-6-iodo-3-amino-2-methylquinazolin-4 (3H)-one (5c). Yield 82%, mp 258°C, IR (cm^{-1}) 3260, 1665, 1595, 1548. ^{1}H NMR ($CDCl_3$) δ: 2.63 (s, 3H, CH_3), 7.03-8.4 (m, 5H, Ar-H), 8.96 (s, 1H, =CH). 10.63(s, 1H, OH). Anal. Calcd. for $C_{16}H_{10}N_3O_2I_3$: N, 6.39, I, 57.99 Found : N, 6.52, I, 57.75.

3-(2-Hydroxy-3,5-dibromobenzalamino)-6-iodo-3-amino-2-methylquinazolin - 4 (3H)-one (5d). Yield 72%, mp 260°C, IR (cm^{-1}) 3412, 1664, 1593, 1560. ^{1}H NMR ($CDCl_3$) δ: 2.62 (s, 3H, CH_3), 7.04-8.4 (m, 5H, Ar-H), 8.84 (s, 1H, =CH). 10.58 (s, 1H, OH). Anal. Calcd. for $C_{16}H_{10}N_3O_2IBr_2$: N, 7.46, % of I & Br , 50.97 Found : N, 7.58, % of I & Br , 50.81.

3-(2-Hydroxy-3,5-dichlorobenzalamino)-6-iodo-3-amino-2-methylquinazolin-4 (3H)-one (5e). Yield 86%, mp 265°C, IR (cm^{-1}) 3420, 1663, 1592, 1520. ^{1}H NMR ($CDCl_3$) δ: 2.63 (s, 3H, CH_3), 7.02-8.6 (m, 5H, Ar-H), 8.98 (s, 1H,= CH). 10.66 (s, 1H, OH). Anal. Calcd. for $C_{16}H_{10}N_3O_2ICl_2$: N, 8.86, % of I & Cl , 41.77 Found : N, 8.54, % of I & Cl , 41.32.

3-(3-Bromo-4-hydroxy-5-methoxybenzalamino)-6-bromo-3-amino-2-methylquinazolin-4(3H)-one (5f). Yield 76%, mp 265°C, IR (cm^{-1}) 3420, 1667, 1597, 1522. ^{1}H NMR (DMSO-d_6) δ: 2.48 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.25-7.82 (m, 5H, Ar-H), 8.76 (s, 1H, =CH).10.54 (s, 1H, OH). Anal. Calcd. for $C_{17}H_{13}N_3O_3Br_2$: N, 8.99, Br, 34.26. Found : N, 9.42, Br, 33.95.

3-(3-Iodo-4-hydroxy-5-methoxybenzalamino)-6-bromo-3-amino-2-methylquinazolin-4 (3H)-one (5g). Yield 69%, mp 270°C, IR (cm^{-1}) 3420, 1669, 1594, 1510. ^{1}H NMR (DMSO-d_6) δ: 1.58 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 7.25-7.82 (m, 5H, Ar-H),8.77(s, 1H, =CH). 10.52 (s,

1H, OH). Anal. Calcd. for $C_{17}H_{13}N_3O_3IBr$: N, 8.17, % of I & Br , 40.27. Found : N, 8.60, % of I & Br , 39.87.

3-(2-Hydroxy-3,5-diiodobenzalamino)-6-bromo- 3 - amino-2-methylquinazolin -4 (3H) - one (5h). Yield 89%, mp 230°C, IR (cm^{-1}) 3412, 1667, 1593, 1520. ^1H NMR ($CDCl_3$) δ: 2.65 (s, 3H, CH_3), 7.13-8.24 (m, 5H, Ar-H), 8.98 (s, 1H, =CH). 10.64(s, 1H, OH). Anal. Calcd. for $C_{16}H_{10}N_3O_2I_2Br$: N, 6.88, % of I & Br , 54.57 Found : N, 7.15, % of I & Br , 54.25.

3-(2-Hydroxy-3,5-dibromobenzalamino)-6-bromo-3-amino-2-methylquinazolin-4 (3H)-one (5i). Yield 78%, mp 250°C, IR (cm^{-1}) 3420, 1669, 1597, 1510. ^1H NMR ($CDCl_3$) δ: 2.64 (s, 3H, CH_3), 7.23-8.26 (m, 5H, Ar-H), 8.94 (s, 1H, =CH). 10.66 (s, 1H, OH). Anal. Calcd. for $C_{16}H_{10}N_3O_2Br_3$: N, 8.13,Br, 46.51 Found : N, 7.82, Br, 46.12.

3-(2-Hydroxy-3,5-dichlorobenzalamino)-6-bromo-3-amino-2-methylquinazolin-4(3H)-one (5j). Yield 79%, mp 264°C, IR (cm^{-1}) 3420, 1669, 1590, 1520. ^1H NMR ($CDCl_3$) δ: 2.62 (s, 3H, CH_3), 7.10-8.12 (m, 5H, Ar-H), 8.95 (s, 1H, =CH). 10.68 (s, 1H, OH). Anal. Calcd. for $C_{16}H_{10}N_3O_2Cl_2Br$: N, 9.61, % of Cl & Br , 34.55 Found : N, 9.98, % of Cl & Br , 34.15.

Acknowledgements

The authors are thankful to UGC New Delhi, India for sanctioning a Major Research Grant and The Director, IICT Hyderabad for providing spectral data. The authors are also thankful to Dr. N.V. Kalyankar, Principal, Yeshwant Mahavidyalaya, Nanded for providing laboratory facilities

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