Action of Some Heterocyclic Amines and Difunctional Nucleophiles on N-Phenylsulphonyloxytetrachlorophthalimide

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Abstract

N-phenylsulphonyloxytetrachlorophthalimide (1) is found to be a useful intermediate for the synthesis of tetrachloroquinazoline derivatives. Quinazolindiones have demonstrated utility in a diverse range of medical and biological applications. Treatment of compound (1) with the appropriate heterocyclic amines and diamines gave a new set of 3-substituted tetrachloroquinazoline via Lossen Rearrangement. The aim of the present study is the synthesis of new quinazoline derivatives via a new synthetic route. The newly synthesized compounds were characterized by IR, 1H NMR and mass spectral studies. The synthesized compounds were evaluated for their preliminary in vitro antibacterial activity towards Salmonella typhi, Staphylococcus aureus, and Bacillus cereus.

Keywords: N-phenylsulphonyloxytetrachlorophthalimide; 2-amino-5-methyl-1,3,4-thiadiazole; Sulphadiazine; 3-aminooquinazolin-2,4-dione; Nucleophilic Attack; Internal Condensation Reaction

1. Introduction

Pyrimidine and quinazoline rings are present in a large number of biologically important compounds such as alkaloids, drugs, antimicrobial agents. Since the early years of this century, numerous studies on the synthesis and structure-activity relationships of pyrimidine and quinazoline derivatives have been reported (Brown, 1994). Also, in recent years, quinazolindiones template, occur in a large number of bioactive molecules, have drawn much attention and interest due to their wide range of biological and pharmacological activities (Hayao et al, 1965; Imagawa & Sakai, 1986; Meuldermans et al, 1988; Russell et al, 1988; Russo et al, 1991; Chao et al, 1999; Mounetou et al, 2001; Boyles et al, 2002; Kakuta et al, 2003 and Tran et al, 2007). Indeed, quinazolindiones have demonstrated utility in a diverse range of medical and biological applications. Accordingly, the aim of the present manuscript is the synthesis of new quinazoline derivatives via a new synthetic route (Scheme 1).

2. Experimental

2.1. Instrumentation

The main experimental challenge appears to be in fine tuning of experimental parameters (solvent, ratio of reagents, catalysis, etc.) so that pure crystalline material can be isolated. 1H NMR (200 MHz) spectra were recorded on a Varian EM 390 spectrometer. Chemical shift values were recorded in δ units (ppm) relative to TMS as internal standard. Melting points were determined by using an electric melting point apparatus (Koffler). Infrared spectra (IR) were recorded using KBr pellets on a Shimadzu 408 spectrometer. Electron impact mass spectra were obtained at 70 eV using a GCMS sp.1000 Shimadzu. The absorption spectra of the different solutions of some synthetic compounds were recorded on Shimadzu 2401 PC spectrophotometer using 1-cm matched quartz cells at
room temperature (≈ 25 °C). Total energy and heat of formation were calculated using the semiempirical AM1 method. Thin layer chromatography (TLC) was performed on silica gel 60 PF254 plates from Merck. Elemental analyses were carried out at Microanalysis Unit at Cairo University, Egypt.

2.2. Chemical Procedure

2.2.1. General Procedure for the Preparation of Substituted (Hetero)tetrachloroquinayplin-2,4-dione (2a-h)

A mixture of N-phenylsulphonyloxytetrachlorophthalimide (compound 1) (Schemes 2 and 4) (0.5 gm, 1.13 mmol) and heterocyclic amines, namely, 2-aminopyridine, 2-aminothiazole, 3-amino-4H-1,2,4-triazole, 2-amino-1,3,4-thiadiazole, 2-amino-5-methyl-1,3,4-thiadiazole, 2-aminobenzothiazole, sulphadiazine and 3-aminoquinazolin-2,4-dione (1.15 mmol) in glacial acetic acid (20 ml). Sodium acetate is then added to this solution as a basic catalyst. This solution is boiled under reflux for 7-12 hours. After cooling, the reaction mixture was poured on ice water, where a solid formed was filtered off and crystallised from appropriate solvent. A precipitate forms slowly, it is removed by filtration. The desired compound is air dried giving 3-substituted (1H, 3H) tetrachloroquinazolin-2,4-diones (2a-h) (Table 1).

2.2.2. Reaction with Ethanolamine

2.2.2.1. Synthesis of 1-acetoxyl-2-[(1H, 3H) tetrachloroquinazolin-2,4-dion-3-yl]ethane (4)

To a solution of N-phenylsulphonyloxytetrachlorophthalimide (0.5 gm, 1.13 mmol) in glacial acetic acid, ethanolamine was added in the presence of anhydrous sodium acetate (0.12 gm, 1.5 mmol) (20 ml) and the reaction mixture was refluxed for 7 hours. After cooling; the reaction mixture was poured on ice water, then the solid product formed was filtered off and crystallised from benzene to give compound number 4 (Scheme 4).

2.2.2.3. Reaction with Aminoethanethiol Hydrochloride

2.2.2.3.1. Synthesis of 2-[(1H,3H)tetrachloroquinazolin-2,4-dion-3-yl]ethanthiol (5)

When a mixture of N-phenylsulphonyloxytetrachlorophthalimide (0.5 gm, 1.13 mmol) and aminoethanethiol hydrochloride undergoes reflux for 7 hours. After cooling, the reaction mixture was poured on ice cold HCl (1:1), where a solid product was precipitated, which was removed by filtration to give the desired compound 5 (Scheme 4).

2.3. Characterisation Data

2.3.1. 3-(2-pyridyl)(1H, 3H)tetrachloroquinazolin-2,4-dione (2a)

White crystal (0.28 gm, 76 %), m.p. >300. FT-IR (KBr, cm-1): 3200 (NH), 1720, 1680 (C=O). 1HNMR spectrum: (200 MHz, DMSO-d6): 7.48-7.56 (ddd (J2,1= 5 Hz, J2, 3= 8 Hz), H-2 and H-4 pyridine), 8.02-8.08 (ddd (J3, 2= 8 Hz, J3,1= 1 Hz, J3,4= 7 Hz), 1H, H-3 pyridine) , 8.61-8.63 (dd (J1,2= 5 Hz, J1,3= 1Hz), 1H, H-1 pyridine) , 11.1 (s, 1H, NH). Anal. calcd. for C13H5Cl4N3O2: C, 41.32; H, 1.33; N, 11.37. Found: C, 41.85; H, 1.34; N, 11.51%.

Total energy = -103489.60 KCal/mol. Heat of Formation= 15.745 KCal/mol.
Scheme 2

Scheme 3
### Table 1. Preparation of Substituted (hetero)tetrachlorquinaylipin-2,4-dione (2a-h)

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<th>Entry</th>
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<th>Time (hr)</th>
<th>Yield (%)</th>
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<tr>
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<tr>
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<td></td>
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<tr>
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</table>
2.3.2. 3-(2-thiazolyl)(1H,3H)tetrachloroquinazolin-2,4-dione (2b)

Pale yellow crystal (0.16 gm, 42 %), m.p. >300. FT-IR (KBr, cm⁻¹): 3200 (NH), 1750, 1650 (C=O). 1HNMR spectrum: (200 MHz, DMSO-d₆): 7.87 (d, 1H, H-5 thiazole), 7.96 (d, 1H, H-4 thiazole), 11.5 (s, 1H, NH). Anal. calcd. for C₁₁H₃Cl₄N₃O₂S: C, 34.49; H, 0.79; N, 10.97. Found: C, 34.75; H, 0.81; N, 10.97 %. Total energy = -101434.53 KCal/mol. Heat of Formation= 14.882 KCal/mol.

2.3.3. 3-(1,2,4-triazol-3-yl)(1H,3H)tetrachloroquinazolin-2,4-dione (2c)

Snowlike crystal (0.22 gm, 60 %), m.p. >300. FT-IR (KBr, cm⁻¹): 3180 (NH), 1730, 1660 (C=O). 1HNMR spectrum: (200 MHz, DMSO-d₆): 8.72 (s, 1H, CH), 11.4 (s, 1H, NH), 14.4 (s, 1H, NH). Anal. calcd. for C₁₀H₃Cl₄N₅O₂: C, 32.73; H, 0.82; N, 19.08. Found: C, 33.03; H, 0.81; N, 19.25 %. Total energy = -103512.79 KCal/mol. Heat of Formation= 53.130 KCal/mol.

2.3.4. 3-(1,3,4-thiadiazol-2-yl)(1H,3H)tetrachloroquinazolin-2,4-dione (2d)

Yellow crystal (0.23 gm, 59 %), m.p. >300. FT-IR (KBr, cm⁻¹): 3400 (NH), 1740, 1680 (C=O). 1HNMR spectrum: (200 MHz, DMSO-d₆): 8.22 (s, 1H, CH), 11.62 (s, 1H, NH). Anal. calcd. for C₁₀H₂Cl₄N₄O₂S: C, 31.28; H, 0.52; N, 14.59. Found: C, 31.46; H, 0.53; N, 14.52 %. Total energy = -102920.05 KCal/mol. Heat of Formation= 38.165 KCal/mol. \( \lambda_{\text{max}} = 386 \text{ nm (Optical Density}= 0.449) \).

2.3.5. 3-(2-methylthiadiazol-5-yl)(1H,3H)tetrachloroquinazolin-2,4-dione (2e)

Pale yellow crystal (0.25 gm, 64 %), m.p. >300. FT-IR (KBr, cm⁻¹): 3240 (NH), 1740, 1660 (C=O). 1HNMR spectrum: (200 MHz, DMSO-d₆): 8.72 (s, 1H, CH), 11.65 (s, 1H, NH). Anal. calcd. for C₁₁H₄Cl₄N₄O₂S: C, 33.20; H, 1.01; N, 14.12 %.

2.3.6. 3-(2-benzothiazolyl)(1H,3H)tetrachloroquinazolin-2,4-dione (2f)

Pale yellow crystal (0.26 gm, 61 %), m.p. 270. FT-IR (KBr, cm⁻¹): 3350 (NH), 1750, 1685 (C=O). 1HNMR spectrum: (200 MHz, DMSO-d₆): 7.57-8.22 (m, 4H, H aromatic), 11.61 (s, 1H, NH). Anal. calcd. For C₁₅H₅Cl₄N₃O₂S: C, 41.60; H, 1.16; N, 9.90. Found: C, 41.67; H, 1.17; N, 10.2 %.

2.3.7. 3-[4-(2-pyrimidyl)aminosulphophenyl](1H,3H)tetrachloroquinazolin-2,4-dione (2g)

White crystal (0.36 gm, 67 %), m.p. >300. FT-IR (KBr, cm⁻¹): 3272, 3108 (NH’s), 3032 (CH arom.), 1740, 1690 (C=O), 1370, 1180. (SO₂). 1HNMR spectrum: (200 MHz, DMSO-d₆): 7.1 (t, 1H, H-5), 7.54-8.14 (dd, 2H, aromatic. H), 8.55 (s, 1H, NH), 11.65 (s, 1H, NH). Anal. calcd. for C₁₈H₉Cl₄N₅O₄S: C, 40.55; H, 1.70; N, 13.14. Found: C, 40.74; H, 1.85; N, 13.25 %. \( \lambda_{\text{max}} = 386 \text{ nm (Optical Density}= 0.449) \).

2.3.8. 3-(3-quinazolyl-2,4-dione)(1H,3H)tetrachloroquinazolin-2,4-dione (2h)

White crystal (0.36 gm, 67 %), m.p. >300. FT-IR (KBr, cm⁻¹): 3272, 3108 (NH’s), 3032 (CH arom.), 1740, 1690 (C=O), 1370, 1180. (SO₂). 1HNMR spectrum: (200 MHz, DMSO-d₆): 7.1 (t, 1H, H-5), 7.54-8.14 (dd, 2H, aromatic. H), 8.55 (s, 1H, NH), 11.65 (s, 1H, NH). Anal. calcd. for C₁₈H₉Cl₄N₅O₄S: C, 40.55; H, 1.70; N, 13.14. Found: C, 40.74; H, 1.85; N, 13.25 %. \( \lambda_{\text{max}} = 386 \text{ nm (Optical Density}= 0.449) \).
molecular ions M, M+2, M+4 and M+6 respectively owing to the presence of four chlorine atoms (Silverstein et al., 1916). Anal. calcd. for C16H6Cl4N4O4: C, 41.77; H, 1.31; N, 12.18. Found: C, 41.99; H, 1.40; N, 12.21 %.

2.3.9. 3-(4-acetylaminophenyl)-5,6,7,8-tetrachloro-1H-quinazolin-2,4-dione (3a)

White crystal (0.35 gm, 71 %), m.p. 322. FT-IR (KBr, cm-1): 3450, 3250 (NHs), 1780, 1750 (C=O). 1HNMR spectrum: (200 MHz, DMSO-d6): 2.07 (s, 3H, CH3), 7.19-7.67 (dd, 4H, arom.H). 10.07 (s, 1H, NH), 11.65 (s, 1H, NH). Anal. calcd. for C16H9Cl4N3O3: C, 44.38; H, 2.10; N, 9.70. Found: C, 44.52; H, 2.00; N, 9.84 %. Total energy = -121031.09 KCal/mol. Heat of Formation= -45.891 KCal/mol.

2.3.10. 7,8,9,10-tetrachloro-(6H,11H)benzimidazo[2,1-b]quinazolin-6-one (3b)
Pale yellow crystal (0.27 gm, 64 %), m.p. >360, FT-IR (KBr, cm-1): 3493 (NH), 3093 (CH), 1751, 1695 (C=O). MS (m/z, %): 371(14.9%) corresponding to the molecular formula C14H5Cl4N3O. in addition to the isotopic characteristic peaks at m/z=373 (16.8%) (M+2), 375(17.9%) (M+4) and 377 (3.0%) (M+6). The solubility of compound 3b was too low to obtain 1H-NMR spectrum in CDCl3 or DMSO-d6. Anal. calcd. for C14H5Cl4N3O: C, 45.09; H, 1.35; N, 11.26. Found: C, 45.24; H, 1.36; N, 11.3 %. Total energy = -99045.58 KCal/mol. Heat of Formation= 67.65 KCal/mol.

2.3.11. 4,4’-bis[tetrachloroquinazolin-2,4-dion-3-yl]biphenyl (3c)

White crystal (0.58 gm, 68 %), m.p. >360. FT-IR (KBr, cm-1): 3272 (NH), 1751, 1695 (C=O). MS (m/z, %): 746 corresponding to the molecular formula C28H10Cl8N4O4. The solubility of compound 3c was too low to obtain 1H-NMR spectrum in CDCl3 or DMSO-d6. Anal. calcd. for C28H10Cl8N4O4: C, 44.85; H, 1.34; N, 7.47. Found: C, 45.02; H, 1.35; N, 7.52 %. Total energy = -203376.80 KCal/mol. Heat of Formation= -13.507 KCal/mol.

2.3.12. 1,6-di(tetrachloroquinazolin-2,4-dion-3-yl)hexane (3d)
Pale yellow crystal (0.4 gm, 62 %), m.p. >360. FT-IR (KBr, cm-1): 3313 (NH), 1736, 1659 (C=O). 1HNMR spectrum: (200 MHz, DMSO-d6): 1.35 (4H, 2CH2), 3.87 (4H, 2CH2-N), 11.13 (s, 1H, NH). Anal. calcd. for C22H14Cl8N4O4: C, 38.75; H, 2.07; N, 8.21. Found: C, 38.96; H, 2.08; N, 8.38 %. Total energy = -186993.68 KCal/mol. Heat of Formation= -112.925 KCal/mol. λmax = 384 nm (Optical Density= 0.173).

2.3.13. Synthesis of 1-acetyloxy-2-[(1H,3H)tetrachloroquinazolin-2,4-dion-3-yl]ethane (4)

White crystal (0.35 gm, 79 %), m.p. >300. FT-IR (KBr, cm-1): 3206 (NH), 2960 (CH aliph.), 1762, 1660 (C=O). 1HNMR spectrum: (300 MHz, DMSO-d6): 1.98 (s, 3H, CH3), 4.14 (t, 2H, CH2-N), 4.25 (t, 2H, CH2-O), 11.19 (s, 1H, NH). MS (m/z, %): 384 (11.58%), 386 (15.81%), 338 (7.3%) and 390 (2.2%) for M, M+2, M+4 and M+6 respectively. Anal. calcd. for C12H8Cl4N2O4: C, 38.75; H, 2.08; N, 8.21. Found: C, 38.96; H, 2.08; N, 8.38 %. Total energy = -111541.74 KCal/mol. Heat of Formation= -131.148 KCal/mol. λmax = 381.5 nm (Optical Density= 0.569).

2.3.14. Synthesis of 2-[(1H,3H)tetrachloroquinazolin-2,4-dion-3-yl]ethanthiol (5)

Yellow crystal (0.22 gm, 55 %), m.p. 210. FT-IR (KBr, cm-1): 3200 (NH), 2960 (CH aliph.), 1742, 1660 (C=O). 1HNMR spectrum: (300 MHz, DMSO-d6): 3.59 (t, 3H, CH2-S), 4.03 (t, H, SH), 4.45 (t, 2H, CH2-N), 11.12 (s, 1H, NH). Anal. calcd. for C10H6Cl4N2O2S: C, 33.36; H, 1.68; N, 7.78. Found: C, 33.65; H, 1.67; N, 7.91 %. Total energy = -94702.40 KCal/mol. Heat of Formation= -46.031 KCal/mol. λmax = 385 nm (Optical Density= 0.334).

3. Biological Activity

Salmonella typhi, Staphylococcus aureus and Bacillus cereus were obtained from the faculty of veterinary medicine, pathology department. The three kinds of selected bacteria were grown on the appropriate media. Compound 2f (Table 1) exhibited antibacterial activity against Salmonella typhi (8 mm) and Staph. Aureus (14 mm). This is due to the four chlorine atoms (Ryan & Ray, 2004) and the pyrimidine ring (Seeley & VanDemank, 1981 and Selassie et al, 1991). It is worthy to mention that compound 2g (Table 1) showed positive antibacterial activity against Salmonella typhi (8 mm) which is (4 mm) less than tetracycline compared to sulphadiazine which has the same effect of tetracycline (12 mm), Bacillus cereus (9 mm). This may be due to the four chlorine (Ryan & Ray, 2004) atoms and the sulphadiazine ring (Emerson, 1993).

Compound 2h (Table 1) and 5 (Scheme 4) have antimicrobial effects against all microorganisms tested.

4. Results and Discussion

The synthetic procedures to obtain the target compounds are depicted in Schemes 2-4. The key intermediate (Schemes 2 and 4) was prepared in a good yield by

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reacting N-hydroxytetra-chlorophthalimide with benzenesulphonyl chloride in pyridine (Hassan et al, 2011). Treatment of compound 1 with the appropriate heterocyclic amines namely, 2-aminopyridine, 2-aminothiazole, 3-amino-4H-1,2,4-triazole, 2-amino-1,3,4-thiadiazole, 2-amino-5-methyl-1,3,4-thiadiazole, 2-amino-benzothiazole, sulphadiazine and 3-aminoquinazolin-2,4-dione (Table1) (1.15 mmol) in sodium acetate and glacial acetic acid. The reaction mixture was refluxed for 7-12 hours. After cooling, the reaction mixture was poured on ice water, where a solid formed was filtered off and crystallised from appropriate solvent to give 3-substituted (1H,3H) tetrachloro-quinazolin-2,4-diones (2a-h) (Scheme 2).

The reaction of N-phenylsulphonyl oxytetrachlorophthalimidewith heterocyclic amines may proceed according to the Lessen Rearrangement (Fahmy et al, 1977).

The reaction of compound 1 with different diamines was intensively investigated; compounds 3a-d (Scheme 3) were prepared by treatment of compound 1 with different diamines namely p-phenylenediamine, o-phenylenediamine, benzidine and hexamethylenediamine (Scheme 3).

The reaction of compound 1 with p-phenylenediamine may proceed according to the Lossen rearrangement followed by acetylation for the NH$_2$ group to give 3a. Also, the reaction of compound 1 with o-phenylenediamine may take place via two mechanistic steps:

i) Nucleophilic attack of one amino group at the carbonyl carbon of compound 1 forming quinazolinedione moiety through ring enlargement Lossen rearrangement.

ii) Internal condensation reaction of the other amino group

The reactions of compound 1 with ethanol amine and aminoethanethiol hydrochloride were investigated as in Scheme 4.

The reaction proceeds through nucleophilic attack of the amino group at the carbonyl carbon of compound 1, followed by Lossen rearrangement to form the quinazoline nucleus and the free OH group, acetylated under the reaction condition.

5. Conclusions

In conclusion, it is worth to mention at this point that there are many features that make tetrachloroquinazolindione very attractive for applications in medicine and biology; these include four chlorine (Ryan & Ray, 2004) atoms and a pyrimidine ring (Nair-Scott et al, 1959 and Selassie et al, 1991). The unique properties of these compounds render them very active compounds against bacteria.

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