Remarkable Conversion of 2-Thioxo-2,3-dihydroquinazolin-4(1H)-ones into the Corresponding Quinazoline-2,4(1H,3H)-diones: Spectroscopic Analysis and X-Ray Crystallography

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A simple and efficient new synthetic method to obtain 3-substituted quinazolin-2,4-diones 9–16 by the reaction of 3-substituted 2-thioxo-quinazolin-4-ones 1–8 with sodamide under mild conditions was presented. The structure of the newly synthesized compounds was determined by infrared spectroscopy, UV-visible spectroscopy, nuclear magnetic resonance, and single-crystal X-ray crystallographic analysis. The crystal structure of 6-methyl-3-phenylquinazoline-2,4(1H,3H)-dione (11) \( [\text{C}_{15}\text{H}_{12}\text{N}_{2}\text{O}_{2}; \text{MF}=252.27, \text{triclinic, P}-1, a=7.8495 (13) \, \text{Å}, b=12.456 (2) \, \text{Å}, c=13.350 (2) \, \text{Å}, \alpha=103.322 (3)^\circ, \beta=90.002 (3)^\circ, \gamma=102.671 (4)^\circ, V=1237.5 (3) \, \text{Å}^3, Z=4, R=0.0592, wR=0.1699, S=1.039] \) was determined. In the crystal cell, two identical conformers of compound 11 were found connected by intramolecular hydrogen bonds, responsible for the favourable occurrence of these two independent molecules.

1. Introduction

The oxidation of thiones into carbonyl compounds has attracted the interest of organic chemists since the early 19th century [1]. Diverse method for this conversion was developed, such as oxidative procedure by organic and inorganic reagents. The oxidation of thiocarbonyl compounds into carbonyl compounds can be performed using different oxidative reagents. Potassium permanganate [2–10] and lead tetra acetate were used to oxidize cyclic thiocarbonate into the corresponding carbonate [8, 11]. The oxidation of thiocarboxylic acid into the corresponding amides was achieved using manganese dioxide, ceric ammonium nitrate, and copper nitrate [12–14]. Hydrogen peroxide and peroxy acids were used to oxidize different thioketones into the corresponding ketones [15, 16]. Conversely, molecular oxygen and ozonation were used to oxidate thione into the corresponding ketones [17–22]. The oxidation of thione compounds into the related carbonyl compounds was achieved using selenium oxide and tin oxides [23–27].

Moreover, quinazolinones, such as quinazolin-2,4-diones, and their corresponding 2-thio-o-quinazolin-4-ones undergo several biological activities, such as carbonic anhydrase [28–31], COX-1/2 [32, 33], tyrosine kinase inhibitors [34], and antitumor activity [35–41]. Due to the biological importance of quinazolin-2,4-diones and 2-thioxo-quinazolin-4-ones, their molecular structures are studied by spectroscopic and theoretical methods [42–46]. Moreover, urea molecule, which constitutes quinazolin-2,4-dione, was extensively studied experimentally and theoretically [47–55]. The crystal form of urea showed a planar conformation, indicating a network of hydrogen bonds [56].

In this study, a new simple methodology was used to oxidate the different quinazolin-2-thiones into the corresponding 2,4-quinazolindione; this was achieved by heating the different quinazolin-2-thiones with sodamide in
methanol. A considerably large amount of yields was afforded. Furthermore, the X-ray crystallography of 6-methyl-3-phenylquinazoline-2,4(1H,3H)-dione (11) was performed, and the configuration of the substituents around the quinazolin-2,4-dione backbone was investigated. Additionally, the spectroscopic interpretation of the synthesized compounds was performed based on ultraviolet-visible (UV-Vis), Fourier transform infrared spectroscopy (FT–IR) and nuclear magnetic resonance (NMR) spectral analysis.

2. Results and Discussion

2.1. Chemistry. As a part of our ongoing program on the development of novel methods for organic synthesis under mild conditions [57], we describe a new efficient and practical route for the one-step conversion of 3-substituted 2-thioxoquinazolin-4-ones (I–8, Table 1) into the corresponding 3-substituted quinazolin-2,4-diones (9–16, Table 1) using sodamide in methanol under mild conditions with high yields (79%–86% yield). To the best of our knowledge, the applicability of sodamide in the synthesis of quinazolidione from quinazolinethione has not been reported (Table 1). The mechanism for the oxidation of quinazolinethione into the corresponding quinazolidione may proceed through the formation of in situ generated sodium peroxide. Different spectral data as well as the X-ray crystallography of compound 11 were used to confirm 3-substituted quinazoline-2,4(1H,3H)-diones. The amide moiety (CONH) of 3-substituted quinazoline-2,4(1H,3H)-diones 11 and 13 was verified by 1H NMR spectra with a peak for the amido proton at 11.47 and 10.87 ppm and by 13C NMR spectra with characteristic peaks at 162.20 and 160.90 ppm for the carbonyl groups with the disappearance of thioamide protons (CSNH) of 3-substituted 2-thioxo-2,3-dihydropyrimidin-4(1H)-ones 3 and 5 at 12.87 and 10.12 ppm and typical thione peaks at 175.50 and 176.50 ppm in 1H NMR and 13C NMR spectra, respectively (Supplementary material (S1 and S2)).

2.2. Experimental UV-Vis and Fourier Transform Infrared Spectroscopy (FT-IR). The UV-Vis and IR spectra of compounds 3 and 11 are shown in Table 2. The UV-Vis analysis of compounds 3 and 11 were performed using methanol and dichloromethane. The UV-Vis absorbance bands for compounds 3 and 11 at the UV region in methanol were 343.0 and 345.4 nm, respectively, whereas the bands in dichloromethane were 344.8 and 349.4 nm, respectively. These bands are the allowed π-π* transitions of the arene rings and the forbidden n-π* transitions of the carbonyl and thiocarbonyl groups. Compounds 3 and 11 (Table 2) exhibited three peaks within the highest peak region in the FT–IR spectrum, the first was NH group stretching vibrations (3248 and 3196 cm⁻¹, respectively), the second was the stretching vibrations of the CH-aromatic ring (3033 and 3050 cm⁻¹, respectively), and the third was the stretching vibrations of CH₂-aliphatic part (2901 and 2940 cm⁻¹, respectively). The two carbonyl groups (2C=O) of compound 11 exhibited two characteristic bands in the FT–IR spectrum; one showed a strong band at 1727 cm⁻¹, whereas the second group exhibited a weak band at 1634 cm⁻¹. Contrarily, only one carbonyl band vibrated at 1657 cm⁻¹ for compound 3. Additionally, the C=O bonds showed two vibrations at 1515 and 1448 cm⁻¹ for compound 11 and 1522 and 1498 cm⁻¹ for compound 3. The C=S band appeared with derivative 3 with sharp peaks at 1205 cm⁻¹, while derivative 11 was void of this band. The C–C bonds were smaller than C=C vibrations and observed at 1270, 1121, and 1072 cm⁻¹ for derivative 11, whereas it was observed at 1393, 1268, and 991 cm⁻¹ for derivative 3.

2.3. The Crystal Structure of Compound 11. The crystallographic data, data collection, structure refinements, chemical structure, and numbering system of compound 11 are listed and exhibited in Table 3 and Figure 1, respectively (Supplementary material (S3, S4, and S5)). Compound 11 was crystallized with Z = 4 in the space group P – 1, and the crystal structure showed a central quinazoline-2,4-dione connecting to the phenyl ring at position-3 and a methyl group at position-6. The quinazoline-2,4-dione core and 6-methyl moiety were in a coplanar position, whereas the phenyl fragment is located on the orthogonal orientation of the quinazoline-2,4-dione core. The asymmetric unit comprised two independent molecules, 11A and 11B (Figure 1), and all the bond lengths and angles are in normal ranges. In the crystal packing, Figure 2 shows that molecules are linked via two intramolecular hydrogen bonds (Table 4). It was reported that the crystallographic structures that possess more than one molecule in the crystal pack could be used to explain the method of packing the molecules to design a material used in technology. Table 4 exhibits the intramolecular hydrogen bonds in the asymmetric unit in the crystal structure; the independent molecules 11A and 11B are linked via intramolecular O2A···HN1B and HN1A···O2B hydrogen bonds with bond lengths of 2.798 and 2.822 Å, respectively. As exhibited in Figure 1 and Table 5, molecules 11A and 11B possess different orientations as indicated by the dihedral angles between the quinazoline-2,4-dione core and the 3-phenyl. In molecule 11A, the dihedral angles of αC1–N2–C10–C11, αC1–N2–C10–C15, αC8–N2–C10–C11, and αC8–N2–C10–C15 are –113.8°, 67.6°, 70.4°, and –108.2°, respectively, relative to the central quinazoline-2,4-dione. In molecule 11B, as shown in Figure 1 and Table 5, the corresponding angles are 64.5°, –116.5°, –111.8°, and 67.2°, respectively. In molecules 11A and 11B, the geometrical parameters of the quinazoline-2,4-dione core are almost similar.
Table 3: Experimental X-ray details for the structure of 6-methyl-3-phenylquinazoline-2,4(1H,3H)-dione (11).

(A) Crystal data

| Compound | UV-Vis (nm, λ<sub>max</sub>) | IR (cm<sup>-1</sup>, ν) |
|----------|-----------------------------|------------------------|
|          | MeOH CH<sub>2</sub>Cl<sub>2</sub> NH stretching CH aromatic stretching CH aliphatic stretching C=O stretching C=C stretching C=S stretching C-C stretching |
| 3        | 343.0 344.8 3248 3033 2901 1657 1522 1205 1268 991 1393 |
| 11       | 345.4 349.4 3196 3050 2940 1634 1448 — 1121 1072 |

Space group
P-1
Z value
4
D<sub>calc</sub>
1.343 g/cm<sup>3</sup>
F<sub>000</sub>
524.0
μ (Mo Ka)
0.088 mm<sup>-1</sup>

(B) Intensity measurements

| Compound | UV-Vis (nm, λ<sub>max</sub>) | IR (cm<sup>-1</sup>, ν) |
|----------|-----------------------------|------------------------|
|          | MeOH CH<sub>2</sub>Cl<sub>2</sub> NH stretching CH aromatic stretching CH aliphatic stretching C=O stretching C=C stretching C=S stretching C-C stretching |
| 3        | 343.0 344.8 3248 3033 2901 1657 1522 1205 1268 991 1393 |
| 11       | 345.4 349.4 3196 3050 2940 1634 1448 — 1121 1072 |

(C) Structure refinement

| Compound | UV-Vis (nm, λ<sub>max</sub>) | IR (cm<sup>-1</sup>, ν) |
|----------|-----------------------------|------------------------|
|          | MeOH CH<sub>2</sub>Cl<sub>2</sub> NH stretching CH aromatic stretching CH aliphatic stretching C=O stretching C=C stretching C=S stretching C-C stretching |
| 3        | 343.0 344.8 3248 3033 2901 1657 1522 1205 1268 991 1393 |
| 11       | 345.4 349.4 3196 3050 2940 1634 1448 — 1121 1072 |

| Compound | UV-Vis (nm, λ<sub>max</sub>) | IR (cm<sup>-1</sup>, ν) |
|----------|-----------------------------|------------------------|
|          | MeOH CH<sub>2</sub>Cl<sub>2</sub> NH stretching CH aromatic stretching CH aliphatic stretching C=O stretching C=C stretching C=S stretching C-C stretching |
| 3        | 343.0 344.8 3248 3033 2901 1657 1522 1205 1268 991 1393 |
| 11       | 345.4 349.4 3196 3050 2940 1634 1448 — 1121 1072 |

Table 2: UV-Vis and IR spectra of compounds 3 and 11.
**Figure 1:** The ORTEP drawing of the basic crystallographic unit of 6-methyl-3-phenylquinazoline-2,4(1H,3H)-dione (11), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level, and all H atoms are shown as small spheres of arbitrary radii.

**Figure 2:** Molecular packing of compound 11 viewed hydrogen bonds which are drawn as dashed lines along the c axis.
Table 4: Hydrogen-bond geometry of the crystal structure 11 (Å, °).

| D—H···A | D—H | H···A | D····A | D—H···A |
|----------|------|-------|--------|---------|
| N1B—H1BA···O2A | 0.880 | 1.930 | 2.798 | 167.00 |
| N1A—H1AA···O2B | 0.88 (3) | 1.96 (3) | 2.822 (3) | 168 (3) |
| C6A—H6AA···O1B | 0.950 | 2.5800 | 3.511 (3) | 166.00 |
| C6B—H6BA···O1A | 0.950 | 2.6000 | 3.527 (3) | 165.00 |

Symmetry codes: (i) x, y, z+1; (ii) x, y, z−1

Table 5: Important torsion angles of the two independent molecules of the crystal structure 11 (°).

| Atom 1 | Atom 2 | Atom 3 | Atom 4 | Angle (°) |
|--------|--------|--------|--------|-----------|
| C1A    | N2A    | C10A   | C11A   | −113.8 (3) |
| C1B    | N2B    | C10B   | C15A   | 67.6 (3)   |
| C1A    | N2A    | C10A   | C15A   | 64.5 (3)   |
| C1B    | N2B    | C10B   | C15B   | −116.5 (3) |
| C8A    | N2A    | C10A   | C11A   | 70.4 (3)   |
| C8B    | N2B    | C10B   | C15A   | −108.2 (3) |
| C8A    | N2A    | C10A   | C15B   | 67.2 (3)   |

3. Conclusion

A novel methodology for synthesizing quinazolin-2,4-dione derivatives by oxidation of the corresponding 2-thioxo-quinazolin-4-one with sodalime was reported. This oxidation method was simple and versatile and proceeded under mild conditions. Spectroscopic methods investigated the chemical structures of the synthesized compounds. The X-ray crystallography of 6-methyl-3-phenylquinazoline-2,4(1H,3H)-dione (11) was performed. The results of the X-ray crystals of compound 11 were [triclinic, P 1, a = 7.8495 (13) Å, b = 12.456 (2) Å, c = 13.350 (2) Å, α = 103.322 (3)°, β = 90.002 (3)°, γ = 102.671 (4)°, V = 1237.5 (3) Å³, Z = 4, R = 0.0592, wR = 0.1699, S = 1.039]. The asymmetric crystal unit of compound 11 showed two identical conformers (11A and 11B) with slightly different phenyl ring orientations at position 3. The two conformers were connected by intermolecular hydrogen bonding, which is the force that governs the occurrence of these two conformers together with steric force in the crystal pack.

4. Experimental

4.1. Chemistry. Melting points were recorded on a Buchi apparatus (CHB). IR spectra were recorded on a FT–IR Perkin–Elmer spectrometer. UV–Vis analysis was performed using a UV spectrophotometer, model UV-1600 from Shimadzu Corporation, Kyoto, Japan. It was equipped with 1 cm matched quartz cells, and the spectra were recorded using computer-assisted software. NMR (1H and 13C NMR) spectra were recorded on Bruker 500 MHz spectrometer using DMSO-d6 as a solvent, and the chemical shifts were expressed in δ ppm, using TMS as an internal standard. Mass spectra were recorded on an Agilent 6320 ion trap mass spectrometer. X-Ray crystallography was analyzed using Bruker APEX-II charge-coupled device (CCD) diffractometer. The crystallographic data of 6-methyl-3-phenylquinazoline-2,4(1H,3H)-dione (11) were deposited with the Cambridge Crystallographic Data Center, deposition number CCDC 772358. Compounds 1–8 were prepared according to the reported procedures [32, 33, 39–41, 57].

4.1.1. General Method for the Preparation of 3-Substituted Quinazolin-2,4-dione 9–16. A mixture of 3-substituted quinazolinthione (10 mmol) and sodamide (20 mmol, 780 mg) in methanol (15 ml) was heated under reflux for 8–12 h. The reaction mixture was filtered while hot, the solvent was removed under reduced pressure, and the obtained solid, which was soluble in water (10 ml), was neutralized with 10% hydrochloric acid. The afforded solid was filtered, dried, and recrystallized using ethanol.

6-Methyl-3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-dione (11). M.p: <300°C, IR (KBr, cm⁻¹): 3248 (NH), 1657 (C=O), and 1205 (C=S); 1H NMR (DMSO-d6): δ 12.87 (s, 1H), 7.73 (s, 1H), 7.46–7.43 (m, 3H), 7.37 (t, 1H, J = 7.5 Hz), 7.5 Hz), 7.33 (d, 1H, J = 8.0 Hz), 7.17 (d, 2H, J = 7.5), 2.34 (s, 3H); 13CNMR (DMSO-d6): δ 175.6, 159.9, 139.2, 137.5, 136.2, 133.7, 128.7, 128.5, 127.9, 126.7, 115.6, 20.4. Ms; [M+ 268].

6-Methyl-3-phenylquinazoline-2,4(1H,3H)-dione (11). M.p: <300°C, IR (KBr, cm⁻¹): 3196 (NH), 1727, and 1634 (C=O); 1H NMR (DMSO-d6): δ 11.47 (s, 1H), 7.74 (s, 1H), 7.53–7.42 (m, 4H), 7.30 (d, 2H, J = 7.0 Hz), 715 (d, 1H, J = 8.5 Hz), 2.35 (s, 3H); 13CNMR (DMSO-d6): δ 162.2, 150.1, 137.6, 136.2, 135.7, 131.7, 129.0, 128.7, 128.0, 126.9, 115.2, 114.0, 20.2. Ms; [M+ 252].

3-Benzyl-2-mercapto-6-nitroquinazolin-4(3H)-one (5). M.p: <300°C, IR (KBr, cm⁻¹): 3170 (NH), 1695 (C=O), and 1176 (C=S); 1H NMR (CDCl3): δ 10.12 (s, 1H), 9.03 (d, 1H, J = 2.38 Hz), 8.50 (dd, 1H, J = 2.52 & 2.45 Hz), 7.56 (d, 2H, J = 7.35 Hz), 7.34 (t, 2H, J = 7.14 & 6.73 Hz), 7.31 (d, 1H, J = 7.12 Hz), 7.22 (d, 1H, J = 8.89 Hz), 5.78 (s, 2H); 13CNMR (CDCl3): δ 176.50, 158.28, 144.05, 141.81, 135.29, 130.26, 129.06, 128.77, 128.47, 128.01, 127.91, 125.59, 115.45, 49.99; Ms; [M+ 313].

3-Benzyl-6-nitroquinazoline-2,4(1H,3H)-dione (13). M.p: <300°C, IR (KBr, cm⁻¹): 3214 (NH), 1729, and 1652 (C=O); 1H NMR (CDCl3, TFA): δ 10.87 (s, 1H), 9.08 (s, 1H), 8.54 (d, 1H, J = 7.0 Hz), 7.51–7.33 (m, 6H), 5.30 (s, 2H); 13CNMR (CDCl3): δ 160.9, 144.1, 141.7, 134.9, 130.4, 129.9, 129.1, 129.4, 128.7, 128.4, 117.7, 116.8, 115.4, 114.7, 113.2, 110.9, 45.7; Ms; [M+ 297].

4.2. UV-Vis Methodology. The 1 mg/mL of compound 11 in methanol/dichloromethane was prepared as a stock solution. Subsequently, 0.2 mL of either the methanol or dichloromethane stock solution was diluted to 10 mL with each solvent to get a solution containing 20 μg/mL for each solvent. Each final solution was recorded against the corresponding solvent as a blank.
4.3. X-Ray Crystallographic Determination. By slow evaporation, 6-methyl-3-phenylquinazoline-2,4(1H,3H)-dione (11) was obtained as single crystals from the ethanolic solution of the pure compound at room temperature. Data were collected on a Bruker APEX-II CCD diffractometer [58,59], equipped with graphite monochromatic Mo Ka radiation, λ = 0.71073 Å at 100 (2) K. Cell refinement and data reduction were carried out using Bruker SAINT SHELXT [58,59], which was used to solve the structure. The final refinement was carried out by full-matrix least-square techniques with anisotropic thermal data for nonhydrogen atoms on F. CCDC 772358 contains the supplementary crystallographic data for this compound and can be obtained free of charge from the Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif. Materials for publication were prepared using PLATON [60] and mercury [61].

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no potential conflicts of interest.

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Supplementary Materials

S1: NMR_Compd-11. S2: NMR_Compd-13. S3: CCDC 772358. S4: check CIF_PLATON. S5: geometric parameters of the crystal structure. (Supplementary Materials)

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