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Communication

Synthesis and Crystal Structure of 1-(3-Fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one

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Abstract: The base catalyzed intramolecular nucleophilic cyclization of 1-(2-bromobenzoyl)-3-(2-fluorophenyl)thiourea (**1**) in the presence of N,N-dimethyl formamide (DMF) afforded the 1-(3-fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**2**) by an intramolecular nucleophilic substitution S_NAr mechanism. The structure was supported by the spectroscopic data and unambiguously confirmed by the single crystal X-ray diffraction data. It crystallizes in the orthorhombic space group P na2_1 with unit cell dimensions a = 22.430(4), b = 8.1478(16), c = 13.522(3) Å, V = 2471.2(9) Å^3. There are two independent molecules per asymmetric unit that are linked to centrosymmetric AB-dimers via intermolecular N-H…S bonds.

Keywords: quinazolinone; 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones; synthesis

1. Introduction

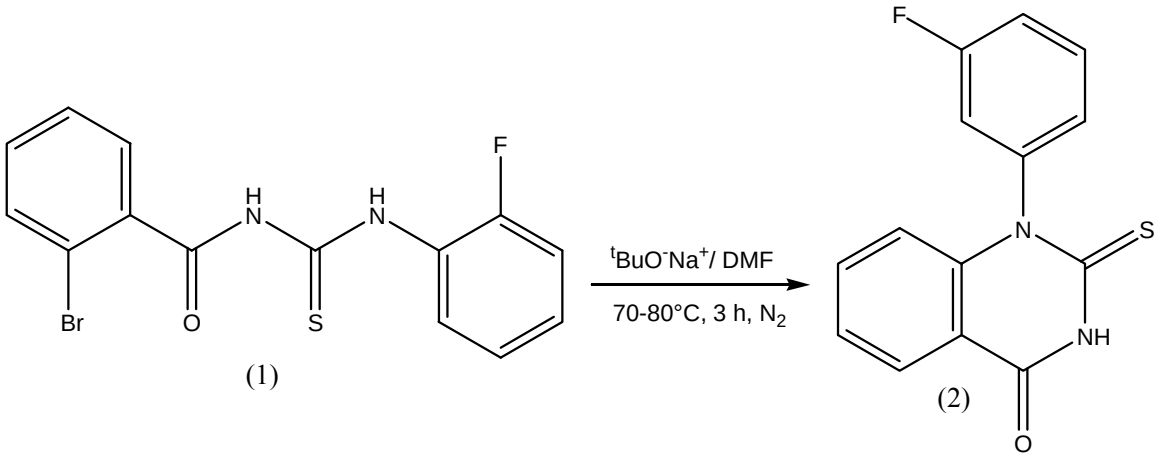
Quinazolinone is the building unit of nearly 150 naturally occurring alkaloids isolated from microorganisms, plants and animals [1]. It is a very important heterocycle exhibiting excellent pharmacological activities such as antimicrobial [2], antifungal [3], antitumor [4], anticancer [5], antiinflammatory [6], antidepressant [7] and anticonvulsant [8] activities. 3-Aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one are a subclass quinazolinones having a wide range of applications including pharmacological and biological activities and important building blocks a variety of

heterocycles [9]. Thus altanserin (3-(2-(4-(4-fluorobenzoyl)-l-piperidinyl)-ethyl)-2,3-dihydro-2-thioxo-1*H*-quinazolin-4-one) and nitroaltanserin are used as drugs for 5-HT2A receptor antagonists [10]. 2-Thioxo-1*H*-4-quinazolinones are also versatile intermediates for fused heterocycloquinazolines like 2-phenyl-5*H*-[1,3,4]thiadiazolo[2,3-b]quinazolin-5-one, 3-(4-bromo phenyl)-2*H*,6*H*-[1,3,4]thiadiazino- [2,3-b] quinazolin-6-one, 4-amino-2-phenyl-3a,4-dihydro-2*H*-thiazolo[3,2-a]quinazoline-1,5-dione and 2-phenyl-[1,3,4]thiadiazino[2,3-b] quinazoline-3,6(2*H*,4*H*)-diones [11]. Two approaches for the solution-phase parallel synthesis of 2-thioxoquinazolin-4-ones include the reaction of methyl anthranilates with isothiocyanates in refluxing pyridine or DMF and reacting 2-(methylcarboxy)-benzene isothiocyanates in isopropyl alcohol with different aliphatic amines or anilines [12]. Herein we report a convenient method for synthesis of these compounds by base catalyzed intramolecular nucleophilic cyclization of 1-aroyl-3-arylthioureas.

2. Results and Discussion

The reaction sequence leading to the formation of title heterocycle is outlined in Figure 1. The base catalyzed intramolecular nucleophilic cyclization of 1-(2-bromobenzoyl)-3-(2-fluorophenyl)thiourea (**1**) was achieved using sodium tertiary butoxide in the presence of dry DMF by heating at 70–80 °C for 3 h under nitrogen to afford (**2**) which was recrystallized from ethanol as colorless crystals.

Figure 1. Synthesis of 1-(3-fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one.



IR spectral data of (**2**) shows the characteristic single broad N-H peak in the range 3265 cm^{-1} and a sharp C=O peak at 1650 cm^{-1} which are relatively at higher wave number compared to the parent thiourea; aromatic absorptions appear at 1603 cm^{-1}, while those for C-S and C-N at 1249 cm^{-1} and 1136 cm^{-1} respectively. ^{1}H-NMR shows characteristic broad singlet for N-H at δ 10.8 in addition to those due to aromatic protons at δ 6.55–8.3 ppm [13]. In ^{13}C-NMR spectrum characteristic peaks for C=S appears downfield as compared to C=O in contrast to the trend in thioureas where the C=O resonates at relatively low field while the C=S resonates up field; thus C=S appears at δ 177, C=O appears at δ 168.9 and C-F couplings appear in the range $^{1}J_{C\text{-}F}$ = 247 Hz, $^{2}J_{C\text{-}F}$ = 22–24 Hz, $^{3}J_{C\text{-}F}$ = 6–14 Hz and $^{4}J_{C\text{-}F}$ = 3.75 Hz.

There are two crystallographically independent molecules A and B per asymmetric unit which exhibit almost equal geometries. Both the fluorophenyl rings make dihedral angles of 86.3(1)° (A) and

82.6(1)° (B) with the corresponding quinazoline planes. C=O and S=O bond lengths of av. 1.231(4) and 1.666(4) Å, respectively, correspond well to those from CCDC reference JESWEK [14] with equal thioxo group (Figure 2).

In the crystal packing molecules A and B are linked to centrosymmetric AB-dimers (Figure 3) via intermolecular N-H…S hydrogen bonds N12-H…S2 (–x + 0.5, y + 0.5,z – 0.5) with N…S of 3.374(3) Å and N22-H…S1 (–x + 0.5, y – 0.5, z + 0.5) with N…S of 3.272(3) Å, resp.

Figure 2. Molecular structure of (**2**) with the two independent molecules A and B per asymmetric unit. B shows disorder of F substituent with positions F21 and F22. Anisotropic displacement ellipsoids are drawn at the 50% probability level.

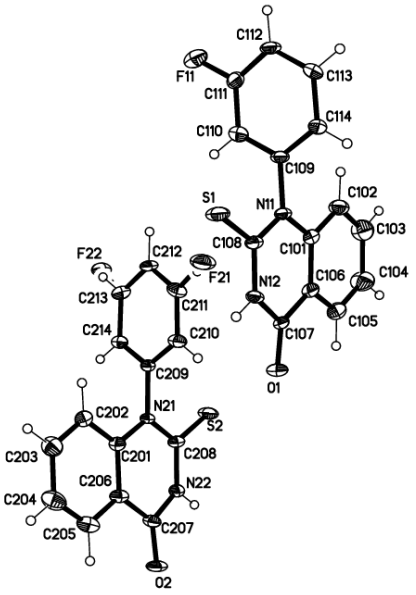
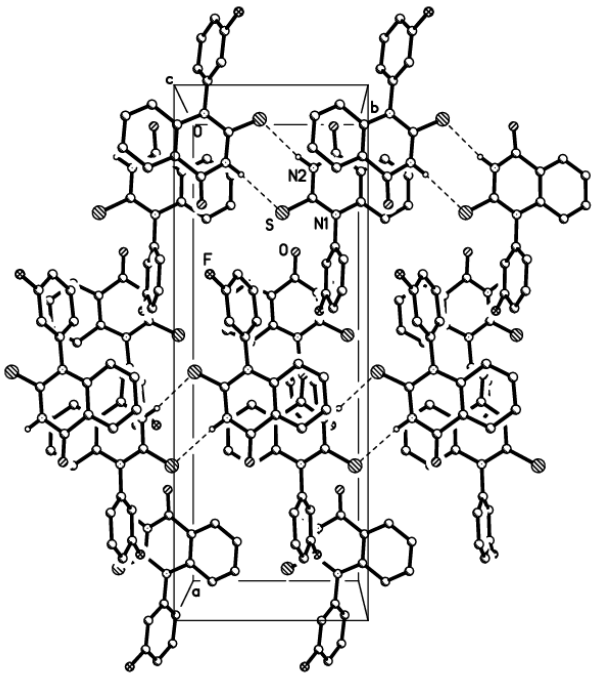


Figure 3. Crystal packing with intermolecular N-H…S interactions. H atoms not involved are omitted.



2.1. Crystal Structure Determination

Data were collected at 120(2) K on a Bruker AXS SMART APEX CCD diffractometer using MoKα radiation. Multi-scan absorption correction with SADABS [15]. Structure solved by direct methods [16], full-matrix least-squares refinement [16] on F^2 for 5877 unique intensities and 354 parameters, all but H atoms refined anisotropically, H atoms from difference Fourier maps refined with riding model on idealized positions with U_{iso} = 1.2 U_{eq}(C/N) and C-H/N-H distances of 0.95/0.88 Å. There are two chemically equal but crystallographically independent molecules A and B per asymmetric unit. Molecule B shows disorder of the fluoro substituent over both *meta*-positions with site occupation factors of 0.671(7) and 0.329(7) for F21 and F22, resp. Experimental data are listed in Table 1.

Table 1. Crystal data and structure refinement for (**2**).

Empirical formula	C_{14} H_9 F N_2 O S
Formula weight	272.29
Temperature	120(2) K
Wavelength	0.71073 Å
Density (calculated)	1.464 Mg/m^3
Absorption coefficient	0.266 mm^{-1}
F(000)	1120
Crystal size	0.39 × 0.31 × 0.29 mm^3
Theta range for data collection	1.82 to 27.88°.
Index ranges	$-29 \le h \le 29$, $-10 \le k \le 10$, $-17 \le l \le 17$
Reflections collected	18748
Independent reflections	5877 [R(int) = 0.0701]
Completeness to theta = 27.88°	100.0%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9268 and 0.9033
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5877/1/354
Goodness-of-fit on F^2	1.038
Final R indices [I > 2σ(I)]	$R1$ = 0.0649, $wR2$ = 0.1439
R indices (all data)	$R1$ = 0.1001, $wR2$ = 0.1638
Absolute structure parameter	0.89(12)
Largest diff. peak and hole	0.971 and –0.325 e $Å^{-3}$
CCDC No.	822489

3. Experimental Section

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. ^{1}H NMR spectra were determined as $CDCl_3$ solutions at 300 MHz using a Bruker Mass Spectra (EI, 70 eV) on a GC-MS instrument. All compounds were purified by thick layer chromatography using silica gel from Merck.

Synthesis of 1-(3-Fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (2)

1-(2-Bromobenzoyl)-3-(2-fluorophenyl)thiourea (**1**) (0.0015 mol), sodium tertiary butoxide (0.0072 mol) and dry DMF (20 mL) were taken in 100 ml three neck round bottom flask fitted with reflux condenser and nitrogen assembly. The reaction mixture was stirred at 70–80 °C for 1–3 h. The progress of reaction was monitored with the help of TLC. When the reaction was completed, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with water, dried and evaporated at rotary evaporator and the solid obtained was re-crystallized from ethanol to afford (**2**) as colourless crystals. (80%): m.p. 203 °C; R_f 0.38 (a); IR (KBr): ν/cm^{-1} 3265 (N-H), 1650 (C=O), 1603 (Ar-C=C), 1249 (C-S), 1136 (C-N); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 10.08 (1H, *br s*, NH), 8.29 (1H, *dd*, *J* = 1.5, 7.8 Hz, Ar-H), 7.67–7.29 (4H, *m*, Ar-H), 7.15 (1H, *d*, *J* = 8.1 Hz, Ar-H), 7.09 (1H, *td*, *J* = 2.1, 8.7 Hz, Ar-H), 6.55 (1H, *d*, *J* = 8.4 Hz, Ar-H); ^{13}C NMR (75 MHz, d^6-DMSO): *δ* 177.1 (1C, C=S), 168.9 (1C, C=O), 157.7 (1C, *d*, $^1J_{C\text{-}F}$ = 247 Hz, Ar-C), 143.4 (1C, Ar-C), 137.1(1C, *d*, ^4J = 3.75, Ar-C), 132.5–122.2 (3C, 3Ar-C), 121.1 (1C, *d*, ^3J = 6.75Hz, Ar-C), 119.8 (1C, *d*, $^2J_{C\text{-}F}$ = 22.5 Hz, Ar-C), 118.9–117.9 (3C, 3Ar-C), 117.6 (1C, *d*, $^3J_{C\text{-}F}$ = 13.5 Hz, 1C, Ar-C), 117.3 (1C, *d*, $^2J_{C\text{-}F}$ = 23.25 Hz, Ar-C); Anal. Calcd. for $C_{14}H_9N_2OSF$: C 61.75; H 3.33; N 10.29; S 11.78%. Found: C 61.79; H 3.35; N 10.21; S 11.71%; GC-MS (m/z): 272 ($M^{\cdot+}$) (100%), 213, 185, 149, 92, 75.

4. Conclusions

Synthesis, characterization, crystal and molecular structure of a novel medicinally and synthetically important heterocycle have been described.

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