A FACILE PREPARATION OF 3-SUBSTITUTED 2-THIOXO-TETRAHYDROQUINAZOLIN-4-ONES BY THE REACTION OF ANTHRANILAMIDE WITH ISOTHIOCYANATES

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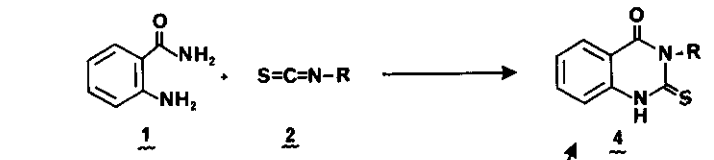
Abstract—3-Substituted 2-thioxo-tetrahydroquinazolin-4-ones (4a-d) can be synthesized in a convenient procedure directly by a treatment of anthranilamide with isothiocyanates at room temperature. However, anthranilamide was reacted with 4-isothiocyanato-1-benzylpiperidine (2e) leading to the formation of 2-[3-(1-benzyl-4-piperidinyl)]thioureidobenzamide (3e) which was subsequently cyclized to 4e under a basic condition.

A convenient approach towards the synthesis of naturally occurring antihypertensive agent doridosine (1-methylisoguanosine) from 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA-ribose) and methyl isothiocyanate has been recently reported.[1] On these grounds we felt that it would be of interest to investigate the reaction of anthranilamide 1 with a variety of isothiocyanates in order to provide a quinazoline structure containing an amino-N-alkyl(aryl)-pyrimidinone moiety for biological interest.[2] In order to synthesize 2-(3-methylthioureido)benzamide (3a) in an initial step for the synthesis of 4-amino-3-methyl-tetrahydroquinazolin-2-one, anthranilamide (1) was treated with methyl isothiocyanate (2a) in acetonitrile at room temperature. Unexpectedly, this reaction afforded a single product which was determined as a bicyclic product 4a instead of the desired thioureido derivative 3a. Compound 4a has been previously prepared either by an alkylation of 2-thioxo-tetrahydroquinazolin-4-one with methyl iodide in a 4% yield,[3] or by a treatment of anthranilic acid with methyl isothiocyanate in 85% yield [3]. However, the reaction described in this manuscript provides a mild and high yield method for the synthesis of 4a.

We report here a convenient and efficient method for the preparation of 3-substituted 2-thioxo-tetrahydroquinazolin-4-ones (4a-f) (Table I) through a reaction of anthranilamide with an excess of isothiocyanates (2a-f) in acetonitrile. This seems to involve an initial nucleophilic addition of the amino group of anthranilamide to the electron deficient carbon of the isothiocyanates 2a-f forming the intermediates 3a-f, of which sp^2 carbon atom of the carboxamide group were subsequently attacked by nucleophilic nitrogen atom of the thioureido moiety, and followed by elimination of the amino group to form compounds 4a-f. The intramolecular displacement between the amide and thioureido functional group in compound 3, the propinquity may play an important role

in the ring closure. In addition to 3-benzyl-2-thioxo-tetrahydroquinazolin-4-one (4c), the isolation of N-benzylthiourea (54%) from the reaction of anthranilamide with benzyl isothiocyanate (2c) lends some support to this proposed mechanism.



2,3	R
a	$-CH_3$
b	$-(CH_2)_3CH_3$
c	$-CH_2$-(2-Cl-phenyl)
d	(2,4-di-Cl-phenyl)
e	(1-benzyl-4-piperidinyl)
f	$-C(=O)$-phenyl

4	R
a	$-CH_3$
b	$-(CH_2)_3CH_3$
c	$-CH_2$-(2-Cl-phenyl)
d	(2,4-di-Cl-phenyl)
e	(1-benzyl-4-piperidinyl)
f	-H

Interestingly, 4-isothiocyanato-1-benzylpiperidine (2e)[4] was treated with anthranilamide in acetonitrile at room temperature to give 2-[3-(1-benzyl-4-piperidinyl)]thioureidobenzamide (3e) in 34% yield. Surprisingly, there is no apparent formation of bicyclic heterocycle 4e even at reflux. Compound 3e was then treated with ethanolic ammonia at room temperature to give 3-[(1-benzyl-4-piperidinyl)]-2-thioxo-tetrathydroquinazolin-4-one (4e) in 67% yield. Similarly, anthranilamide was reacted with benzoyl isothiocyanate (2f) to afford 2-[(3-benzoyl)thioureido]benzamide 3f in 83% yield which was subsequently cyclized to 2-thioxo-tetrahydroquinazolin-4-one (4f)[5] in 50% yield.

The results obtained indicated that the present method appears to be generally and successfully applicable to the preparation of 3-substituted 2-thioxo-tetrahydroquinazolin-4-ones (4). In some

cases, it can be accomplished either via directly from anthranilamide or through the intermediate 3 under a basic conidition. On the other hand, the synthetic approach reported here may be useful in view of the pharmacological interest of this class of compounds.[6]

Table I. 3-Substituted 2-thioxo-tetrahydroquinazolin-4-ones (4) prepared

4	Yield [%]	mp[°C]	Molecular formula[a]	ir(KBr) ν [cm^{-1}]	^{1}H-nmr (DMSO-d_6) δ [ppm]
a	77	248-250[3]	$C_9H_8N_2OS$ (192.2)	1690, 1620	1.3 (s, 3H), 7.0-8.0 (m, 4H), 12.8 (s, 1H)
b	67	172	$C_{12}H_{14}N_2OS$ (234.4)	1648, 1625	0.9 (t,3H), 1.0-1.8 (m, 4H), 4.4 (t, 2H), 7.2-8.0 (m, 4H), 12.8 (s, 1H).
c	98	249-250	$C_{15}H_{12}N_2OS$ (268.3)	1689, 1620	5.7 (s, 2H), 7.1-8.0 (m, 9H), 12.9 (s, 1H).
d	67	289-290	$C_{14}H_8N_2OS$ (323.2)	1661, 1614	7.2 (m, 7H), 13.4 (s, 1H).
e	67	249-251	$C_{20}H_{21}N_3OS$ (351.4)	1693, 1666	1.5-3.1 (m, 8H), 3.5 (s, 2 H), 5.8 (s, 1H), 6.9-8.1 (m, 9H), 12.8 (s, 1H).
f	50	295-296[5]			6.9-8.1 (m, 4H), 12.3 (s, 1 H), 12.5 (s, 1H).

a Satisfactory microanalyses were obtained: C ± 0.17%, H ± 0.24%, N ± 0.17%

General Procedure

Melting points were obtained on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer. ^{1}H nuclear magnetic resonance spectra were recorded on a Joel FX-100 spectrometer from National Taiwan Normal University, Taipei, using DMSO-d_6 as solvent and as internal standard. Elemental analysis was carried out on Heraeus Elemental Analyzer in Cheng-Kong University, Tainan.

Preparation of 3-substituted 2-thioxo-tetrahydroquinazolin-4-ones (4a-d); General Procedure:

To a solution of anthranilamide (1.36 g, 10 mmol) in acetonitrile (30 ml) was added methyl isothiocyanate (1.46 g, 20 mmol). The solution was stirred at room temperature for 24 h. The solid was collected by filtration and washed with ether (5 ml). The crude products were recrystallized from acetonitrile.

2-[3-(1-Benzyl-4-piperidinyl)]thioureidobenzamide (3e); Typical reaction:

To a solution of anthranilamide (1.36g,10 mmol) in acetonitrile (30 ml) was added 4-isothiocyanato-1-benzylpiperidine (4.65 g, 20 mmol). The solution was stirred at room temperature and the reaction mixture became a suspension after 2 h. After 24 h, the solid was collected by filtration

and washed with ether (10 ml). The crude product was recrystallized from a mixture of dimethylformamide and water (V:V, 3:7) to give 3e; yield: 1.25g (34%); mp 164-166°C ; ir (KBr): ν =1672 (C=O) cm^{-1}; ^{1}H-nmr(DMSO-d_6): δ 1.40 (m,2H,CH_2); 1.66 (m,2H,CH_2); 2.06 (m,2H,CH_2); 2.72 (m,2H,CH_2); 3.50 (s,2H,Ar-CH_2); 3.99 (d,1H,N-H); 7.05-7.61 (m,9H,Ar-H); 8.12 (s,2H,NH_2); 8.70 (s,1H,N-H); 10.46 (s,1H,N-H); Anal. Calcd. for $C_{20}H_{23}N_4OS$ (367.4): C, 65.38; H,6.31; N,15.25. Found: C, 65.31; H, 6.56; N,15.40.

3-[(1-Benzyl-4-piperidinyl)]-2-thioxo-tetrahydroquinazolin-4-one (4e):

A suspension of compound 3e (0.85 g, 20 mmol) in ethanol (20 ml) and 33% aqueous ammonia (60 ml) was stirred at room temperature for 48 h. The white solid was collected by filtration. The crude product was dissolved in 1N sodium hydroxide and treated with activated charcoal, then filtered. The filtrate was acidified with acetic acid at pH 6 to give 4e.

2-(3-Benzoyl)thioureidobenzamide (3f):

A mixture of anthranilamide (1.36 g, 10 mmol) and benzoyl isothiocyanate (2g, 12 mmol) in acetonitrile (30 ml) was stirred at room temperature for 1h. The solid was collected by filtration. The crude solid was recrystallized from acetonitrile to give 3f; yield: 2.5 g (83%); mp 202-204°C; ir (KBr): ν =1649 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.1-7.8 (m,7H,Ar-H+NH_2); 7.8-8.1 (m,4H,Ar-H); 11.47 (s,1H,NH); 13.06 (s,1H,NH); Anal. Calcd: for $C_{15}H_{13}N_3O_2S$ (299.3):C, 60.19; H, 4.38; N, 14.0. Found: C, 60.17; H, 4.30; N, 13.78.

2-Thioxo-tetrahydroquinazolinone (4f):

A mixture of 2g (1.3g, 4 mmol) in ethanol (20 ml) and 33% aqueous ammonia (60 ml) was stirred at room temperature for 48 hours. The brown solid was collected by filtration and was recrystallized from acetonitrile to give 4f.

ACKNOWLEDGEMENT

The authors gratefully acknowledge a grant No. NSC75-0412-B016-66 from Nation Science Council of the Republic of China on Taiwan for supporting this research.

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Received, 24th July, 1987