Diheterocyclic Compounds from Dithiocarbamates and Derivatives Thereof. VII. 1-(2-Benzazolylaminophenylsulphonyl)-4-[4-oxo-2-thioxo(oxo)-1,2,3,4-tetrahydro-3-quinazolinyl]benzenes

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Received February 13, 1995

Bisheterocycles **8** with two different heterocyclic rings attached to the central benzene nucleus are readily synthesized from dithiocarbamic acid derivatives **4** or **5**, using compound **1** as the starting material.

J. Heterocyclic Chem., **32**, 1181 (1995).

For several years we have reported the preparation of difunctionalized derivatives of the dithiocarbamic acid starting from arylenediamines and its further usefulness in the synthesis of bisbenzazoles and other bisheterocycles with application as model compounds of polyheterocyclic systems [1,2,3,4].

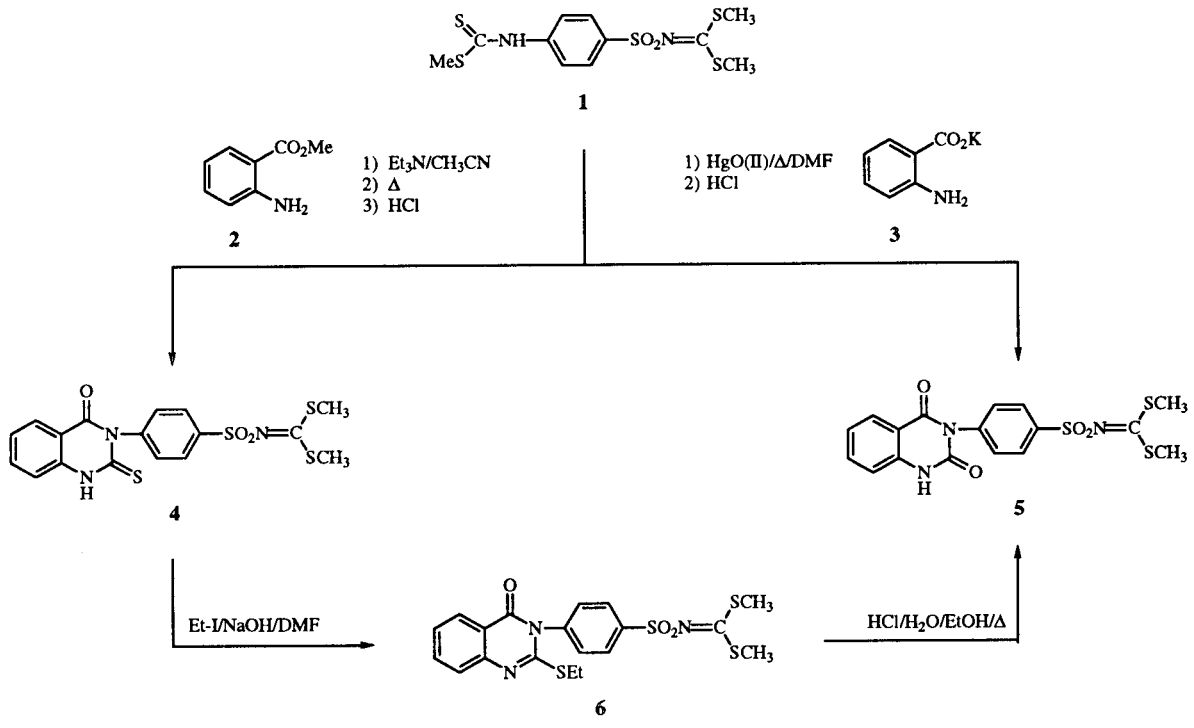
We have previously reported a new methodology for the synthesis of unsymmetrical bisbenzazoles in which the different reactivity of the two-NH_2 moieties of sulphanilamide is exploited thus providing a new entry to bis(benzazolyl)sulphanylamides [5]. As a continuation of our work, the synthesis of the title compounds was undertaken.

We wish now to report here a new synthetic approach for the preparation of bisheterocycles with two different heterocyclic rings attached to the central benzene nucleus in a protocol which involves the use of dimethyl *N*-(4-thiomethylthiocarbonylaminophenylsulphonyl)dithiocarbonoiomidate **1** [5] derived from sulphanilamide. Structures containing both quinazoline and azole rings have been synthesized in two steps.

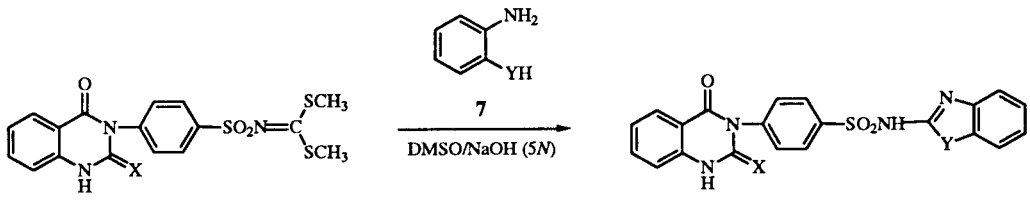
The stepwise formation of the quinazoline rings starting from the difunctional derivative **1** is illustrated in Scheme I. Compound **1** turned out to be very well suited to our approach. When **1** was treated with methyl anthranilate **2** in the presence of triethylamine and heated in acetonitrile as a solvent, quinazoline **4** was obtained after acidification in good yield. On the other hand, the reaction of **1** with potassium anthranilate **3** in the presence of red mercury(II) oxide at 70° in dimethylformamide only afforded quinazoline **5** in lower yield.

Compound **5** could be readily obtained from **6**, which in turn was prepared from **4** by treatment with ethyl iodide in the presence of aqueous sodium hydroxide at room

Scheme I



Scheme II



temperature in dimethylformamide and subsequent acidic hydrolysis with 6*N* hydrochloric acid.

The synthesis of compounds **8** was carried out from **4** or **5** as shown in Scheme II. When **4** or **5** was made to react with *o*-aminothiophenol, *o*-aminophenol and *o*-phenylenediamine in a basic medium 1-(2-benzazolylaminophenylsulphonyl)-4-[4-oxo-2-thioxo(oxo)-1,2,3,4-tetrahydro-3-quinazolinyl]-benzenes were obtained (Table 1).

Table 1

1-(2-Benzazolylaminophenylsulphonyl)-4-[4-oxo-2-thioxo(oxo)-1,2,3,4-tetrahydro-3-quinazolinyl]benzenes

Compound	X	Y	mp (°C) [a]	Yield (%)
8a	S	S	>300	65
8b	S	O	>300	84
8c	S	NH	>300	78
8d	O	S	>300	58
8e	O	O	>300	70
8f	O	NH	>300	58

[a] All compounds were recrystallized in a mixture of DMF/H_2O.

The structures of all compounds were determined on the basis of their ^{1}H nmr spectra (coupling pattern of the aromatic protons and the chemical shift of the hydrogen-bonded amino group).

In conclusion, the readily availability of the dithiocarbamic acid derivatives provides a straightforward route for the synthesis of 1,4-disubstituted sulphanylamides with two different heterocyclic rings, *i.e.* benzazole and quinazoline. This methodology represents the complement for the preparation of unsymmetrical N^1,N^4-bis(2-benzazolyl)sulphanylamides [5] as well as a wide variety of unsymmetrical systems.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer FT 1600 instrument. The ^{1}H-nmr spectra were recorded on a Varian 300 Unity spectrometer with TMS as internal reference.

Dimethyl *N*-[4-(4-Oxo-2-thioxo-1,2,3,4-tethrahydro-3-quinazolinylphenylsulphonyl)]dithiocarbonoimidate **4**.

A solution of **1** (6.00 g, 0.016 mole) in acetonitrile (5 ml) was treated with triethylamine (1.81 g, 0.018 mole) at room temperature, stirred for 30 minutes and refluxed for 1 hour. Then, a solution of **2** (2.41 g, 0.016 mole) in acetonitrile (10 ml) was added dropwise and the mixture was refluxed until no more methylmercaptan was evolved (approximately 23 hours). After cooling, the mixture was neutralized with 5*N* hydrochloric acid. The precipitate thus obtained was filtered, washed with diethyl ether and dried, yield 4.36 g (73%), mp 298-300°; ir (Nujol): 3243-3070, 1661, 1463, 1157 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.10 (br s, 1H), 8.01 (d, 2H, J = 8.4 Hz), 7.94 (dd, 1H, J = 1.3 Hz), 7.79 (td, 1H, J = 8.2, 1.3 Hz), 7.55 (d, 2H, J = 8.4 Hz), 7.44 (d, 1H, J = 8.2 Hz), 7.35 (td, 1H, J = 8.2, 1.0 Hz), 2.60 (s, 6H).

Anal. Calcd. for $C_{17}H_{15}N_3O_3S_4$: C, 46.66; H, 3.45; N, 9.60. Found: C, 46.79; H, 3.56; N, 9.48.

Dimethyl *N*-[4-(2,4-Dioxo-1,2,3,4-tethrahydro-3-quinazolinylphenylsulphonyl)]dithiocarbonoimidate **5**.

Method A.

To a suspension of **3** (0.005 mole) and red mercury(II) oxide (1.50 g, 0.0075 mole) in dimethylformamide (15 ml) with vigorous stirring at room temperature, was added a solution of **1** (1.87 g, 0.005 mole) in dimethylformamide (15 ml). The mixture was heated for 22 hours at 70°, cooled and filtered. The filtrate was poured into water (300 ml), cooled in an ice-bath and acidified (*p*H = 3-4) with concentrated hydrochloric acid. The precipitate formed was isolated by filtration, washed with water, ethanol, diethyl ether and dried, yield, 0.65 g (31%).

Method B.

Dimethyl *N*-[4-(4-Oxo-2-ethylthio-3,4-dihydro-3-quinazolinylphenylsulphonyl)]dithiocarbonoimidate **6**.

A solution of **4** (1.48 g, 0.0034 mole) in dimethylformamide (10 ml) was treated with aqueous 5*N* sodium hydroxide (0.7 ml, 0.0034 mole) at room temperature and the mixture was stirred for 1 hour. Then, ethyl iodide (0.0034 mole) was added dropwise and the resulting mixture was stirred for 2 hours. After cooling, the precipitate was filtered, washed with ethanol and dried, yield, 1.13 g (71%), mp 197-199°; ir (Nujol): 1689, 1608, 1452, 1156 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.10-7.40 (m, 8H), 3.11 (q, 2H, J = 7.0 Hz), 2.61 (s, 6H), 1.20 (t, 3H, J = 7.0 Hz).

Anal. Calcd. for $C_{19}H_{19}N_3O_3S_4$: C, 49.00; H, 4.11; N, 9.02. Found: C, 49.21; H, 4.28; N, 9.13.

To a solution of **6** (2.18 g, 0.0047 mole) in ethanol (20 ml) was added 6*N* hydrochloric acid (18 ml), and refluxed for 6 hours. After cooling, the precipitate obtained was filtered,

washed with water, ethanol, ether and dried, yield, 1.82 g (92%), mp 260-262°; ir (Nujol): 3236-3142, 1730, 1650, 1470, 1157 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.6 (s, 1H), 8.01 (d, 2H, J = 8.8 Hz), 7.93 (dd, 1H, J = 8.3, 1.5 Hz), 7.70 (ddd, 1H, J = 8.0, 7.0, 1.5 Hz), 7.48 (d, 2H, J = 8.8 Hz), 7.22 (m, 2H), 2.60 (s, 6H).

Anal. Calcd. for $C_{17}H_{15}N_3O_4S_3$: C, 48.43; H, 3.58; N, 9.97. Found: C, 48.61; H, 3.62; N, 9.78.

1-[2-Benzazolylaminophenylsulphonyl-4-(4-oxo-2-thioxo(oxo)-1,2,3,4-tethrahydro-3-quinazolinyl)]benzenes **8**.

General Procedure.

A solution of the corresponding **7** (1 mmole) in DMSO (4 ml) was treated with aqueous 5*N* sodium hydroxide (0.40 ml, 2 mmoles) at room temperature and the mixture was stirred for 30 minutes. Then a solution of the corresponding **4** or **5** (1.00 mmole) in DMSO (5 ml) was added dropwise and the mixture was refluxed under nitrogen until no more methylmercaptan was evolved (approximately 16 hours). After cooling, the mixture was treated with hydrochloric acid (*p*H = 4-5) and poured into a bath of ice-water (200 ml). The precipitate thus obtained was filtered, washed with water, ethanol, diethyl ether, dried and recrystallized.

1-[2-Benzothiazolylaminophenylsulphonyl-4-(4-oxo-2-thioxo-1,2,3,4-tethrahydro-3-quinazolinyl)]benzene **8a**.

The yield was 65%, mp >300° (DMF/H_2O); ir (Nujol): 3170-3108, 1664, 1623, 1464, 1142 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.1 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 8.00-7.73 (m, 3H), 7.55 (d, 2H, J = 8.4 Hz), 7.55-7.20 (m, 6H).

Anal. Calcd. for $C_{21}H_{14}N_4O_3S_3$: C, 54.05; H, 3.02; N, 12.01. Found: C, 54.27; H, 3.19; N, 12.21.

1-[2-Benzoxazolylaminophenylsulphonyl-4-(4-oxo-2-thioxo-1,2,3,4-tethrahydro-3-quinazolinyl)]benzene **8b**.

This compound was obtained in 84% yield, mp >300° (DMF/H_2O); ir (Nujol): 3240, 1662, 1621, 1559, 1152 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.1 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 7.92 (d, 1H, J = 7.9 Hz), 7.76 (td, 1H, J = 8.6, 1.6 Hz), 7.60 (d, 2H, J = 8.4 Hz), 7.50-7.20 (m, 7H).

Anal. Calcd. for $C_{21}H_{14}N_4O_4S_2$: C, 55.98; H, 3.13; N, 12.43. Found: C, 56.16; H, 3.27; N, 12.56.

1-[2-Benzimidazolylaminophenylsulphonyl-4-(4-oxo-2-thioxo-1,2,3,4-tethrahydro-3-quinazolinyl)]benzene **8c**.

This compound was obtained in 78% yield, mp >300° (DMF/H_2O); ir (Nujol): 3375-3245, 1662, 1620, 1536, 1161 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.1 (s, 1H), 7.80-7.32 (m, 14H).

Anal. Calcd. for $C_{21}H_{15}N_5O_3S_2$: C, 56.10; H, 3.36; N, 15.58. Found: C, 55.91; H, 3.49; N, 15.79.

1-[2-Benzothiazolylaminophenylsulphonyl-4-(2,4-dioxo-1,2,3,4-tethrahydro-3-quinazolinyl)]benzene **8d**.

This compound was obtained in 58% yield, mp >300° (DMF/H_2O); ir (Nujol): 3264, 1731, 1673, 1617, 1466, 1146 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.6 (s, 1H), 7.95 (d, 2H, J = 8.5 Hz), 7.92 (dd, 1H, J = 8.2, 1.3 Hz), 7.80 (dd, 1H, J = 7.9, 1.5 Hz), 7.69 (dd, 1H, J = 8.2, 1.5 Hz), 7.53 (d, 2H, J = 8.5 Hz), 7.55-7.20 (m, 6H).

Anal. Calcd. for $C_{21}H_{14}N_4O_4S_2$: C, 55.98; H, 3.13; N, 12.43. Found: C, 56.17; H, 3.28; N, 12.61.

1-[2-Benzoxazolylaminophenylsulphonyl-4-(2,4-dioxo-1,2,3,4-tethrahydro-3-quinazolinyl)]benzene **8e**.

This compound was obtained in 70% yield, mp >300° (DMF/H_2O); ir (Nujol): 3259, 1731, 1650, 1625, 1462, 1148 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.6 (s, 1H), 8.04 (d, 2H, J = 8.5 Hz), 7.91 (dd, 1H, J = 8.5, 1.3 Hz), 7.69 (dd, 1H, J = 7.9, 1.5 Hz), 7.54 (d, 2H, J = 8.5 Hz), 7.51 (d, 1H, J = 8.5 Hz), 7.37-7.20 (m, 6H).

Anal. Calcd. for $C_{21}H_{14}N_4O_5S$: C, 58.05; H, 3.24; N, 12.89. Found: C, 58.21; H, 3.12; N, 12.71.

1-[2-Benzimidazolylaminophenylsulphonyl-4-(2,4-dioxo-1,2,3,4-tethrahydro-3-quinazolinyl)]benzene **8f**.

This compound was obtained in 58% yield, mp >300° (DMF/H_2O); ir (Nujol): 3363, 3262, 3135, 1731, 1673, 1630, 1450, 1159 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.6 (s, 1H), 7.92-7.17 (m, 14H).

Anal. Calcd. for $C_{21}H_{15}N_5O_4S$: C, 58.18; H, 3.48; N, 16.16. Found: C, 58.34; H, 3.31; N, 16.32.

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