REACTION OF 4-THIOXO-1,3-BENZOTHIAZINES WITH AMIDRAZONES: SYNTHESIS OF 1,2,4-TRIAZOLO[1,5-c]QUINAZOLINE DERIVATIVES

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Abstract - *2-Aryl-4-thioxo-1,3-benzothiazines react with unsubstituted amidrazones to give the corresponding amidinoquinazolinthiones which by action of methyl iodide cyclize to 2,5-diaryl-1,2,4-triazolo[1,5-c]quinazolines. Reaction of amidinoquinazolinthiones with hydrochloric acid leads to 2,5-diarylthiadiazoles.*

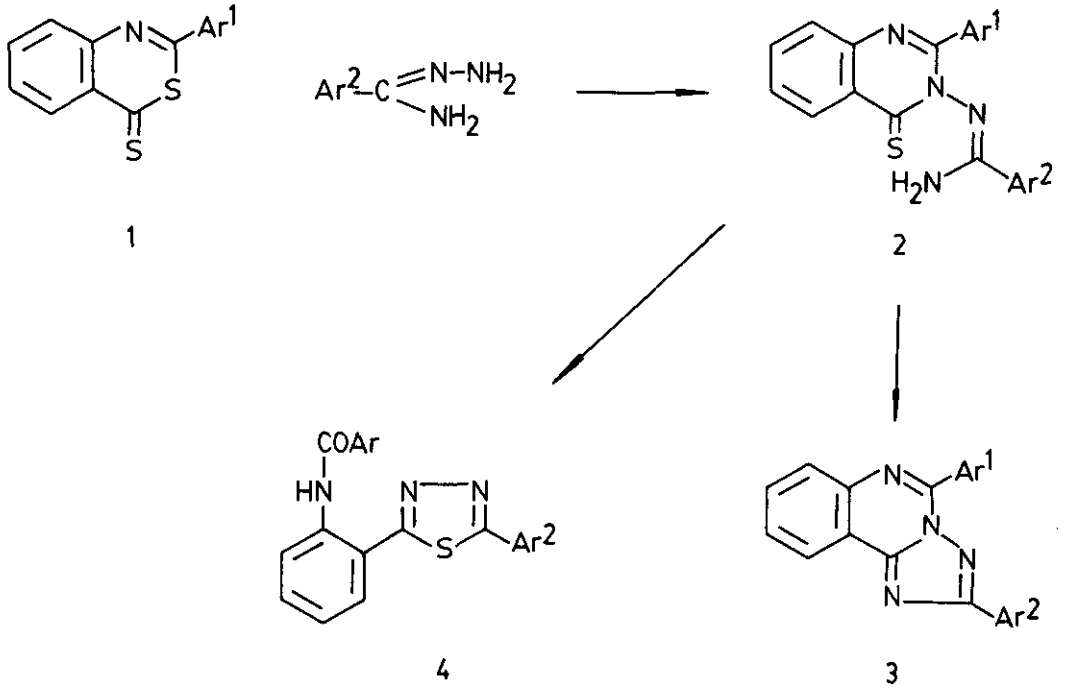
No generally useful procedure for the synthesis of 1,2,4-triazolo[1,5-c]quinazoline derivatives has hitherto been reported, only two methods have been briefly mentioned for their preparation: the first involves treatment of 4-oxo-4*H*-3,1-benzoxazine with aminoguanidine and provided a suitable route to 2-amino-1,2,4-triazolo[1,5-c]quinazoline[1]. The second method involves reaction of 4-quinazolylhydrazine with aliphatic acids or rearrangement of the isomeric 1,2,4-triazolo[4,3-c]quinazoline, available from 4-quinazolylhydrazine and ortho esters, by acid or heat[2].

The reaction of primary amino groups with 4-thioxo-1,3-benzothiazines to give the corresponding 3-substituted-4-thioxo-3,4-dihydroquinazolines has been reported[3] and recently we have studied the reaction with thiocarbohydrazide to give 1,3,4-triazolo[3,2-c]quinazoline derivatives which display mesoionic character[4]; however reactions of 4-thioxo-1,3-benzothiazines with 1,2-bifunctional nitrogen nucleophiles such as amidrazones have not been reported. We now report a convenient preparation of 1,2,4-triazolo[1,5-c]quinazolines by reaction of 3-aryl-4-thioxo-1,3-benzothiazines 1 with unsubstituted amidrazones.

Compounds 1, readily available from 2-aryl-4-oxo-4*H*-3,1-benzoxazines and phosphorus pentasulfide[5], react with aryl unsubstituted amidrazones at reflux temperature in ethanol in the presence of triethylamine for 21 h, giving the corresponding amidinoquinazolinthiones 2 as crystalline solids in moderate yields.

Structures 2 are based on microanalytical data and spectral evidence. In the Ir spectra, the compounds show absorption bands for the amino group at 3480-3370 cm^{-1}. Mass spectra show the expected molecular ion peaks in high abundance; peaks are also found at M^+-16 for the loss of the amino group, and at M^+-33 for the loss of the mercapto group.

When treated with excess of methyl iodide in ethanol at room temperature for 12-24 h, the amidinoquinazolinthiones 2 underwent cyclization to give the corresponding 2,5-diaryl-1,2,4-triazolo[1,5-c]quinazolines 3 which were isolated as crystalline solids. The cyclization reaction was found to depend on the nature of the Ar^2 substituent, attempted cyclization of compounds 2c, 2d, 2g and 2h failed to give 3. On the other hand, when compounds 2 were treated with hydrochloric acid in ethanol at reflux temperature, the corresponding 2,5-diarylthiadiazoles 4 were isolated in good yields (65-60%). We believe that this conversion involves initial protonation of the amino group followed by cyclization and elimination of ammonia to give the highly reactive[4] 1,3,4-thiadiazolo[3,2-c]quinazolin-4-ium chloride which under the reaction conditions undergoes ring-opening to give 4. Structural elucidation of compounds 3 and 4 is accomplished by elemental analysis and spectral data. Compounds 4 are identified by Ir and ^{1}H Nmr spectral comparison with authentic specimens[6].



EXPERIMENTAL

Melting points were obtained on a Kofler hot-stage apparatus, and are uncorrected. Ir spectra were run using NaCl plates on a Nicolet FT-5DX spectrophotometer in Nujol emulsions. ^{1}H Nmr spectra were obtained on a Varian EM-360A 60 MHz spectrometer. Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer. Elemental analyses were performed with a Perkin-Elmer 240C instrument.

Table I. Preparation of Amidinoquinazolinthiones 2.

Entry	Ar^1	Ar^2	Mp (°C)	Yield (%)	Crystal form	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	C_6H_5	C_6H_5	153-155	60	Yellow prisms	70.58	4.46	15.81	$C_{21}H_{16}N_4S$	70.76	4.53	15.72
b	C_6H_5	$4\text{-}H_3C\text{-}C_6H_4$	178-180	58	Orange prisms	71.28	4.84	15.16	$C_{22}H_{18}N_4S$	71.33	4.90	15.12
c	C_6H_5	$4\text{-}O_2N\text{-}C_6H_4$	194-196	52	Pink prisms	63.04	3.65	17.32	$C_{21}H_{15}N_5O_2S$	62.83	3.77	17.44
d	C_6H_5	2-pyridyl	193-195	63	Yellow prisms	67.38	4.17	19.68	$C_{20}H_{15}N_5S$	67.21	4.23	19.59
e	$4\text{-}H_3C\text{-}C_6H_4$	C_6H_5	133-135	25	Green prisms	71.47	4.81	15.24	$C_{22}H_{18}N_4S$	71.33	4.90	15.12
f	$4\text{-}H_3C\text{-}C_6H_4$	$4\text{-}H_3C\text{-}C_6H_4$	174-176	50	Yellow prisms	72.04	5.16	14.63	$C_{23}H_{20}N_4S$	71.85	5.24	14.57
g	$4\text{-}H_3C\text{-}C_6H_4$	$4\text{-}O_2N\text{-}C_6H_4$	205-207	66	Orange prisms	63.45	4.16	16.71	$C_{22}H_{17}N_5O_2S$	63.60	4.13	16.86
h	$4\text{-}H_3C\text{-}C_6H_4$	2-pyridyl	140	67	Orange prisms	67.85	4.39	18.72	$C_{21}H_{17}N_5S$	67.90	4.61	18.85

Table II. Preparation of 1,2,4-Triazolo[1,5-c]quinazolines 3.

Entry	Ar^1	Ar^2	Mp (°C)	Yield (%)	Crystal form	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	C_6H_5	C_6H_5	154-156	67	red prisms	78.16	4.31	17.41	$C_{21}H_{14}N_4$	78.24	4.38	17.38
b	C_6H_5	$4\text{-}H_3C\text{-}C_6H_4$	206-208	70	white prisms	78.60	4.74	16.51	$C_{22}H_{16}N_4$	78.55	4.79	16.66
c	$4\text{-}H_3C\text{-}C_6H_4$	C_6H_5	128-130	64	brown prisms	78.40	4.65	16.79	$C_{22}H_{16}N_4$	78.55	4.79	16.66
d	$4\text{-}H_3C\text{-}C_6H_4$	$4\text{-}H_3C\text{-}C_6H_4$	165-168	63	white prisms	78.92	5.24	15.79	$C_{23}H_{18}N_4$	78.83	5.18	15.99

Table 3. Spectral Data of Compounds 2 and 3.

Compound No.	IR (cm^{-1})	^1H-NMR[a] (ppm)	MS[b] m/e (%)
2a	3471, 3369, 1630, 1591, 1557, 1404, 1315, 1313, 1291, 1228, 1047, 1024, 866, 769, 713, 701, 662.	9.1-7.2 (14H, m) 5.2 (2H, s)	357(M^++1, 19), 356(M^+, 77), 340(100), 323(23), 279(14), 223(5), 205(21) 121(5), 120(11), 77(11).
2b	3449, 3307, 1619, 1602, 1591, 1551, 1296, 1228, 1074, 945, 866, 826, 764 730, 696, 684, 662.	9.2-7.1 (13H, m) 5.2 (2H, s) 2.38 (3H, s)	371(M^++1, 21), 370(M^+, 82), 354(61), 337(24), 336(13), 335(8), 279(7), 253(70), 235(87), 205 (28), 136(100).
2c	3471, 3432, 3369, 3307, 3228, 3199, 1630, 1574, 1523, 1342, 1319, 1285, 951, 860, 764, 696.	9.0-7.3(aromatic ,m)	402(M^++1, 28), 401(M^+, 100), 386(20), 385(80), 368(23), 339(8), 279(6), 223(3), 205(7).
2d	3477, 3437, 3307, 1619, 1562, 1449, 1308, 1257, 1200, 1024, 945, 798, 764, 747, 722, 691, 672.	8.8-7.2 (13H, m) 6.55 (2H, s)	358(M^++1, 2), 357(M^+, 19), 324(35), 279(14), 223(16), 205(22), 121 (40), 120(100), 119(12).
2e	3454, 3307, 3239, 3216, 1630, 1596, 1557, 1410, 1319, 1296, 1223, 1047, 1024, 871, 815,781, 764, 724, 701.	9.0-7.1 (13H, m) 5.2 (2H, s) 2.32 (3H, s)	371(M^++1, 21), 370(M^+, 82), 369(14), 355(28), 354(100), 337(29), 336 (18), 293(11), 235(13), 219(20).
2f	3466, 3307, 3239, 3211, 1625, 1591, 1557, 1511, 1415, 1319, 1291, 1223, 945, 871, 832, 815, 764, 724, 661.	9.4-7.3 (12H, m) 5.4 (2H, s) 2.4 (3H, s) 2.35 (3H, s)	385(M^++1, 22), 384(M^+, 81), 383(11), 369(28), 368(100), 351(24), 293 (91), 219(10).

Table 3. (continuation).

2g	3483, 3426, 3360, 3313, 1630, 1579, 1545, 1517, 1506, 1342, 1178, 1104, 1042, 945, 866, 858, 822, 773, 698.	9.3-7.2 (12H, m) 5.6 (2H, s) 2.38 (3H, s)	416(M^++1, 27), 415(M^+, 100), 414(12), 400(26), 399((90), 382(23), 336 (10), 219(5).
2h	3488, 3375, 1613, 1551, 1200, 1177, 1024, 951, 815, 764, 741, 718.	9.1-7.15 (12H, m) 6.5 (2H, s) 2.4 (3H, s)	372(M^++1, 24), 371(M^+, 91), 370(32), 355(26), 338(100), 293(28), 219 (14).
3a	1653, 1625, 1602, 1523, 1443, 1019, 951, 769, 724, 690.	9.4-7.5(aromatic, m)	323(M^++1, 23), 322(M^+, 100), 321(59), 292(12), 219(12), 205(5), 190(10).
3b	1623, 1613, 1560, 1526, 1449, 1319, 1300, 1274, 1178, 955, 833, 781, 744, 697, 688.	9.1-7.3 (13H, m) 2.45 (3H, s)	337(M^++1, 23), 336(M^+, 100), 335(55), 214(14), 205(5), 190(10), 147(7).
3c	1624, 1615, 1602, 1522, 1509, 1445, 1375, 953, 822, 780, 723, 691.	9.1-7.4 (13H, m) 2.65 (3H, s)	337(M^++1, 25), 336(M^+, 100), 335(60), 306(4), 292(11), 233(12), 219 (4), 205(5).
3d	1613, 1602, 1557, 1528, 1517, 1472, 1455, 1319, 1296, 1274, 1183, 1109, 956, 945, 826, 785, 741, 724.	9.1-7.4 (12H, m) 2.55 (3H, s) 2.45 (3H, s)	351(M^++1, 26), 350(M^+, 100), 349(60), 233(16), 219(8), 205(4), 190(8).

[a] Obtained as solutions in $CDCl_3$ except for compounds 2c and 2g which were obtained in DMSO-d_6.

[b] Recorded at 70 eV.

General Procedure for the Formation of Amidinoquinazolinthiones 2

To a solution of the appropriate 3-aryl-4-thioxo-1,3-benzothiazine 1 (4 mmol) in anhydrous ethanol (20 ml), the corresponding amidrazone (4 mmol) and triethylamine (4 mmol) were added. The resultant mixture was stirred at reflux temperature for 21 h. After cooling, the precipitated solid was collected by filtration, dried and recrystallised from ethanol to give 2 (see table I).

General Procedure for the Formation of 1,2,4-Triazolo[1,5-c]quinazolines 3

To a solution of amidinoquinazolinthione 2 (2 mmol) in ethanol (10 ml), methyl iodide (0.35 g, 2.5 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The solution was concentrated under reduced pressure, the precipitated obtained was filtered off and recrystallised from ethanol to give 3 (see Table II).

General Procedure for the Formation of 2,5-Diaryl-1,3,4-thiadiazoles 4

To a solution of amidinoquinazolinthione 2 (1 mmol) in ethanol (10 ml), concentrated hydrochloric acid (1 ml) was added. The resultant mixture was stirred at room temperature for 6h. The precipitated solid was collected by filtration and recrystallised from ethanol to give 4.

ACKNOWLEDGEMENT

The authors are indebted to Comisión Asesora de Investigación Científica y Técnica for financial support, project number 2019/83.

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Received, 31st May, 1985