Reaction of 3-Hetero-substituted 2-Phenyl-4-thioxo-3,4-dihydroquinazolines with Acyl Chlorides and Phenacyl Bromides

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Some 2,5-disubstituted 1,3,4-thiadiazoles **5** were obtained by reaction of 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**1**) with acyl chlorides. Reaction of 3-hydroxy-2-phenyl-3,4-dihydroquinazoline (**3**) with phenacyl bromides was carried out either in dry acetonitrile or dimethylformamide to give 2-phenyl-4-phenacylthio-3-quinazolinium *N*-oxides **7** or 2-phenyl-4-phenacylidene-1*H*-3-quinazolinium *N*-oxides **8**, respectively.

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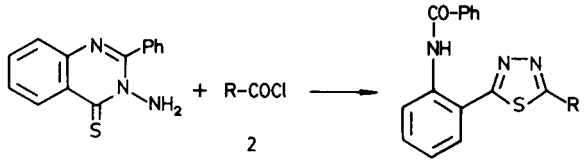
In continutation of the study on the chemistry of 4-oxo-3,4-dihydroquinazoline derivatives [1,2], we have studied the reactions of 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**1**) with acyl chlorides **2** and the 3-hydroxy-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**3**) with phenacyl bromides **4**. The chemistry of **1** remains nearly unexplored; only its preparation and reactions with acetyl chloride [3], carbon disulphide [4] and aromatic aldehydes [2] to give the corresponding *N*-acetylamino derivatives, 1,3,4-thiadiazolo[2,3-*d*]quinazolinium-5-thione and 2,5-disubstituted-1,3,4-thiadiazoles, respectively, have been reported. Similarly, for the compound **3** only its preparation [5] and reactions with metallic cations [6] have been reported.

Compound (**1**) reacts with acyl halides to give 2-substituted 5-(*o*-benzoylamino)phenyl-1,3,4-thiadiazoles **5**, which are isolated as yellow crystals, except for **5g**, in moderate yields and in high purity (Table I). The reaction can be performed by simple heating at 180° under nitrogen of an admixture of **1** and **2** (Method A); when volatile acyl halides have been used the reactions were carried out in sealed tubes under similar reaction conditions (Method B) (Scheme 1). Presumably, the mechanism of formation of **5**



a, R = C_6H_5
b, R = 4-$CH_3C_6H_4$
c, R = 4-ClC_6H_4
d, R = 4-$O_2NC_6H_4$
e, R = 2-naphtyl
f, R = 4-BrC_6H_4
g, R = $CH_3(CH_2)_6$

Scheme 1

Table I

2,5-Disubstituted-1,3,4-thiadiazoles **5**.

Compound	R	Method	Yield (%)	Mp (a)	Molecular Formula	Analyses (%) Calcd. C	H	N	S	Found C	H	N	S
5a	C_6H_5	A	52	188	$C_{21}H_{15}N_3OS$ (357.4)	70.57	4.23	11.76	8.97	70.45	4.12	11.85	8.90
5b	4—$CH_3C_6H_4$	A	54	202	$C_{22}H_{17}N_3OS$ (371.4)	71.15	4.61	11.31	8.63	71.01	4.77	11.52	8.75
5c	4—ClC_6H_4	B	55	168	$C_{21}H_{14}ClN_3OS$ (391.9)	64.36	3.60	10.72	8.18	64.54	3.50	10.64	7.99
5d	4—$O_2NC_6H_4$	A	67	229	$C_{21}H_{14}N_4O_3S$ (402.4)	62.68	3.50	13.92	7.97	62.81	3.40	13.81	7.80
5e	2-naphthyl	A	48	202	$C_{25}H_{17}N_3OS$ (407.5)	73.69	4.20	10.31	7.87	73.82	4.10	10.19	7.80
5f	4—BrC_6H_4	B	51	205	$C_{21}H_{14}BrN_3OS$ (463.3)	57.81	3.23	9.63	7.35	57.69	3.20	9.80	7.62
5g	$CH_3(CH_2)_6$	B	37		$C_{22}H_{25}N_3OS$ (379.5)								

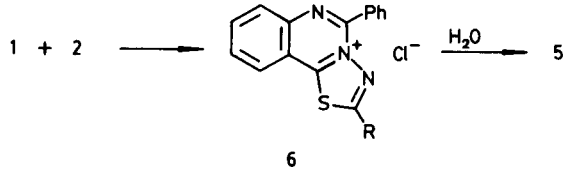
(a) From ethanol.

Table II

Spectral Data of Compounds **5**

Compound	ir, ν (cm^{-1}, Nujol)	ms, m/e (%)
5a	3220-3160, 1685, 1615, 1595, 1540, 1500, 1430, 1315, 1305, 1270, 1070, 770, 745, 705, 680	357 (M^+, 70), 340 (7), 329 (11), 280 (43), 252 (8), 149 (8), 121 (10), 105 (100), 77 (48)
5b	3240-3160, 1680, 1620, 1600, 1505, 1450, 1420, 1315, 1305, 1105, 1000, 830, 760, 745, 710, 660	371 (M^+, 100), 354 (8), 343 (17), 294 (58), 105 (95), 77 (58)
5c	3260-3120, 1680, 1620, 1595, 1550, 1500, 1445, 1420, 1310, 1095, 1000, 840, 760, 740, 705, 650	393 (M^+ +2, 10), 391 (M^+, 28), 374 (6), 363 (10), 314 (14), 286 (6), 238 (6), 149 (7), 105 (100), 77 (45)
5d	3120-3080, 1690, 1620, 1600, 1530, 1420, 1355, 1310, 1110, 830, 760, 730, 700	402 (M^+, 43), 372 (6), 356 (7), 325 (17), 296 (28), 236 (6), 105 (100), 77 (65)
5e	3140-3080, 1690, 1620, 1590, 1550, 1470, 1430, 1310, 1210, 920, 825, 770, 750, 705, 660	407 (M^+, 15), 406 (22), 302 (5), 330 (13), 171 (11), 153 (11), 127 (14), 126 (8), 105 (100), 77 (60)
5f	3120-3060, 1690, 1600, 1480, 1420, 1310, 1080, 1020, 900, 770, 710	
5g	3200-3080, 1680, 1610, 1590, 1530, 1460, 1415, 1300, 970, 760, 705	379 (M^+, 16), 302 (21), 274 (72), 203 (55), 190 (100), 119 (37), 105 (76), 77 (28)

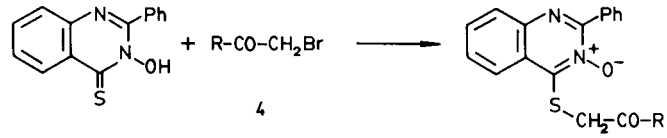
involves the formation of the intermediate **6** which are converted into **5** by reaction with water formed during the initial cyclocondensation step (Scheme 2). Structures **5**



Scheme 2

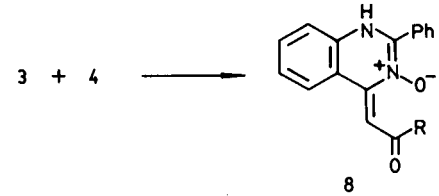
are based on microanalytical data, spectral evidence and comparison with authentic materials (Table II).

On the other hand, compound **3** reacts with α-halocarbonyl compounds **4a-c** in dry acetonitrile at reflux temperature to give 2-phenyl-4-phenacylthio-3-quinazolinium *N*-oxides **7a-c**, which are isolated as yellow crystals in moderate yields (Table III). However, for compounds **7d-e** the reaction must be caried out in dry methanol in the presence of sodium methoxide. Structures **7a-e** are based on microanalytical data and spectral evidence. In the ir spectra, the compounds show absorption bands for the carbonyl group at 1740-1680 cm^{-1} which are in good agreement with reported values for similar types of compounds [7]. In addition, compounds **7a-e** show an absorption band at 1580-1630 cm^{-1} due to the stretching vibration of C=N bond. Mass spectra of **7a-d** do not show the molecular ion peaks, but show the $M^+ - 16$ peak, which serves as a diagnostic test for the *N*-oxide group [8,9]. The ^{1}H-nmr spectra



a, R = 4-BrC_6H_4
b, R = 4-$C_6H_5C_6H_4$
c, R = 4-ClC_6H_4
d, R = 4-$CH_3OC_6H_4$
e, R = CH_3CH_2O

Scheme 3



a, R = 4-BrC_6H_4
b, R = 4-$C_6H_5C_6H_4$
c, R = C_6H_5
d, R = 4-ClC_6H_4
e, R = 4-$O_2NC_6H_4$
f, R = 4-$CH_3OC_6H_4$

Scheme 4

show a singlet at δ = 4.37-5.95 corresponding to the *S*-linked methylene group (—S—CH_2—COR) which are in accordance with reported values for similar compounds [10] (Table IV).

When compound **3** reacts with phenacyl bromides **4** either in dimethylformamide at reflux temperature for 2 hours or in methanol in the presence of sodium methoxide for a short period of time (0.5 hours) the corresponding 2-phenyl-4-phenacylidene-1*H*-3-quinazolinium *N*-oxides **8** are isolated as yellow crystalline solids in good yields (Table V). Support for the formulation of 2-phenyl-4-phen-

Table III

2-Phenyl-4-acylmethylthio-3-quinazolinium *N*-Oxides **7**

Compound	R	Reaction Solvent	Conditions Time (hours)	Yield (%)	Mp °C	Molecular Formula	Analyses (%) Calcd./Found C	H	N	S
7a	4—BrC_6H_4	MeCN	1	61	197 (a)	$C_{22}H_{15}BrN_2O_2S$ (451.4)	58.54 58.75	3.35 3.46	6.21 6.39	7.10 6.92
7b	4—$C_6H_5C_6H_4$	MeCN	14	42	188 (b)	$C_{28}H_{20}N_2O_2S$ (448.5)	74.98 74.77	4.49 4.36	6.25 6.20	7.15 7.01
7c	4—ClC_6H_4	MeCN	3	51	140 (b)	$C_{22}H_{15}ClN_2O_2S$ (406.9)	64.94 65.10	3.71 3.69	6.88 7.01	7.88 7.70
7d	4—$CH_3OC_6H_4$	MeOH/ MeONa	1	68	139 (a)	$C_{23}H_{18}N_2O_3S$ (402.5)	68.63 68.39	4.51 4.32	6.96 7.03	7.96 8.11
7e	EtO	MeOH/ MeONa	7	55	141 (a)	$C_{18}H_{16}N_2O_3S$ (340.4)	63.51 63.42	4.74 4.65	8.23 8.17	9.42 9.30

(a) From methanol/chloroform (1:1). (b) From ethanol.

Table IV

Spectral Data of Compounds **7**

Compound	ir, ν (cm^{-1}, Nujol)	^{1}H-NMR, δ (ppm)	ms, m/e (%)
7a	1700, 1580, 1530, 1480, 1400, 1345, 1310, 1200, 1065, 980, 810, 770, 750, 710	8.27-6.8 (13H, m), 5.54 (2H, s)	436 ($M^+ + 2 - 16$, 11), 434 ($M^+ - 16$, 11), 404 (39), 402 (39), 250 (64), 247 (39), 219 (14), 205 (25), 185 (100), 183 (100), 157 (43), 155 (43), 102 (28), 77 (68)
7b	1680, 1610, 1560, 1540, 1480, 1340, 1310, 1200, 990, 840, 770, 755, 700, 655	8.4-7.0 (18H,m) 5.95 (2H, s)	432 ($M^+ - 16$, 16), 400 (81), 247 (27), 219 (9), 205 (14), 181 (100), 153 (31), 152 (50), 102 (9), 77 (29), 76 (17)
7c	1700, 1630, 1600, 1565, 1510, 1460, 1305, 1220, 1105, 995, 830, 770, 710, 700, 670	8.3-6.9 (13H, m) 5.42 (2H, s)	390 ($M^+ - 16$, 5), 358 (6), 237 (49), 205 (100), 152 (20), 139 (34), 111 (31), 102 (38), 77 (92)
7d	1680, 1610, 1590, 1560, 1470, 1310, 1260, 1220, 1175, 1030, 825, 765, 695	8.36-6.89 (13H, m) 5.05 (2H, s) 3.80 (3H, s)	354 ($M^+ - 16 - 32$, 46), 247 (20), 237 (8), 219 (9), 205 (17), 135 (100), 107 (20), 77 (73)
7e	1740, 1610, 1570, 1550, 1470, 1450, 1310, 1285, 1200, 1170, 1120, 930, 765, 710, 685	8.40-7.35 (9H, m) 4.37 (2H, s) 3.98 (2H, q) 0.98 (3H, t)	340 (M^+, 13), 324 (9), 292 (18), 250 (43), 237 (28), 219 (36), 205 (100), 119 (59), 102 (43), 77 (87)

Table V

2-Phenyl-4-phenacylidene-1*H*-3-quinazolinium *N*-Oxides **8**

Compound	R	Reaction Solvent	Conditions Time (hours)	Yield (%)	Mp °C	Molecular Formula	Analyses (%) Calcd./Found C	H	N
8a	4—BrC_6H_4	DMF MeOH/MeONa	2 0.5	66 92	214-215 (a)	$C_{22}H_{15}BrN_2O_2$ (419.3)	63.02 63.20	3.60 3.64	6.68 6.74
8b	4—$C_6H_5C_6H_4$	DMF MeOH/MeONa	2 0.5	95 61	205 (b)	$C_{28}H_{20}N_2O_2$ (416.5)	80.75 80.91	4.84 4.85	6.73 6.60
8c	C_6H_5	DMF MeOH/MeONa	2 0.5	65 81	156 (b)	$C_{22}H_{16}N_2O_2$ (340.4)	77.63 77.52	4.74 4.53	8.23 8.09
8d	4—ClC_6H_4	DMF MeOH/MeONa	2 0.5	70 91	196 (a)	$C_{22}H_{15}ClN_2O_2$ (374.8)	70.50 70.32	4.03 4.12	7.47 7.32
8e	4—$O_2NC_6H_4$	DMF MeOH/MeONa	2 0.5	96 97	255 (b)	$C_{22}H_{15}N_3O_4$ (385.4)	68.56 68.38	3.92 3.77	10.90 10.76
8f	4—$CH_3OC_6H_4$	MeCN MeOH/MeONa	16 7	60 75	170 (b)	$C_{23}H_{18}N_2O_3$ (370.4)	74.58 74.70	4.90 4.86	7.56 7.49

(a) From benzene. (b) From methanol/chloroform (1:1).

Table VI

Spectral Data of Compounds **8**

Compound	ir, ν (cm^{-1}, Nujol)	^{1}H-NMR, δ (ppm)	ms, m/e (%)
8a	1610, 1585, 1560, 1470, 1350, 1220, 1140, 1070, 1010, 840, 770, 755, 690	8.40-7.30 (13H, m) 6.73 (1H, s)	404 ($M^+ + 2 - 16$, 100), 402 ($M^+ - 16$, 100), 376 (20), 374 (20), 247 (54), 219 (19), 205 (11), 185 (20), 183 (20), 157 (11), 155 (11), 77 (13)
8b	1610, 1580, 1495, 1480, 1370, 1280, 1230, 1170, 1070, 890, 765, 750, 705, 690	8.35-7.20 (18H, m) 6.7 (1H, s)	400 ($M^+ - 16$, 100), 372 (19), 247 (27), 219 (6), 205 (10), 181 (43), 153 (16), 152 (28), 77 (32)
8c	1610, 1595, 1560, 1485, 1470, 1350, 1225, 1140, 1020, 770, 730, 690	8.25-7.18 (14H, m) 6.6 (1H, s)	324 ($M^+ - 16$, 71), 306 (8), 296 (34), 247 (80), 219 (25), 205 (17), 105 (100), 89 (37), 77 (94)
8d	1620, 1560, 1470, 1355, 1220, 1145, 1025, 850, 770, 755, 690, 685	8.45-7.40 (13H, m) 6.66 (1H, s)	358 (M^+, -16, 100), 330 (29), 247 (58), 219 (21), 205 (25), 139 (75), 111 (66), 89 (58), 77 (83)
8e	1610, 1560, 1525, 1470, 1345, 1280, 1225, 1140, 870, 850, 765, 740, 705, 690	8.40-7.35 (13H, m) 6.62 (1H, s)	369 ($M^+ - 16$, 100), 341 (21), 251 (50), 247 (67), 219 (18), 205 (35), 150 (16), 105 (12), 104 (12), 77 (21), 76 (13)
8f	1610, 1560, 1480, 1350, 1260, 1170, 1135, 1020, 840, 795, 780, 765, 690	8.40-7.20 (13H, m) 6.65 (1H, s) 3.78 (3H, s)	354 ($M^+ - 16$, 100), 326 (25), 247 (47), 219 (23), 205 (28), 135 (70), 107 (54), 77 (64)

acylidene-1*H*-3-quinazolinium *N*-oxides **8** is clearly provided by spectral evidence. The ir spectra show absorption at 1610-1620 cm^{-1} for the carbonyl group. Mass spectra do not show the molecular ion peak. The basepeaks appear either at m/e R—CO$^+$ or at m/e $M^+ - 16$; peaks are also found at m/e 205, 219 and 247 for all members of this series. The ^{1}H-nmr spectra show a singlet at δ = 6.6-6.7 ppm corresponding to R—CO—CH= proton. No signal due to the —OH proton has been observed (Table VI).

EXPERIMENTAL

The melting points were determined with a Kofler hot stage microscope and were uncorrected. The ir spectra were recorded in mineral oil mulls with a Perkin-Elmer 457 instrument. ^{1}H nmr spectra were obtained on solutions in deuteriochloroform with tetramethylsilane as the internal standard using a Varian FT-80 instrument. Mass spectra were obtained with a Hewlett-Packard 5980 A gc/ms system; compounds were introduced through the direct insertion probe. The electron beam energy was 70 eV. Microanalysis were performed with a Perkin-Elmer 240 instrument.

2,5-Disubstituted-1,3,4-thiadiazoles **5**. General Procedure.

Method A.

A mixture of the 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**1**) (2.53 g, 10 mmoles) and the appropriate acyl chloride (10 mmoles), was heated at 180° for 4 hours under nitrogen. After cooling the red reaction product was treated with cold ethanol (20 ml) and the separated solid was found to be **5**. By elimination of the solvent from the mother liquor led to a residual product which when treated with aqueous 1*N* sodium hydroxide led to a yellow solid which when recrystallized from ethanol gave **5** (Table I).

Method B.

A mixture of the 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**1**) (2.53 g, 10 mmoles) and the appropriate acyl chloride (10 mmoles) was heated in a sealed tube at 180° for 4 hours. Work-up was similar to the above described method.

2-Phenyl-4-acylmethylthio-3-quinazolinium *N*-Oxides **7**. General Procedure.

To a solution of 3-hydroxy-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**3**) (2.54 g, 10 mmoles) in dry acetonitrile (60 ml), the appropriate phenacyl bromide **4** (10 mmoles) was added. The reaction mixture was stirred under reflux temperature until a solid separated (1-14 hours), which when recrystallized from the appropriate solvent gave **7** (Table III). The preparation of **7d** and **7e** were achieved by reaction of equimolecular amounts of **3** and *p*-methoxyphenacyl bromide or ethylbromoacetate in methanol (60 ml) in the presence of sodium methoxide at reflux temperature for 1 hour.

2-Phenyl-4-phenacylidene-1*H*-3-quinazolinium *N*-Oxides **8**. General Procedure.

Method A.

To a solution of 3-hydroxy-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**3**) (2.54 g, 10 mmoles) in dry dimethylformamide (60 ml) the corresponding phenacyl bromide **4** (10 mmoles) was added. The resultant solution was heated under reflux temperature for 2 hours. After cooling the dark solution was poured into a mixture of ice-water and the precipitated solid separated and was recrystallized from the appropriate solvent to give **8** (Table V).

Method B.

To a solution of 3-hydroxy-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**3**) (2.54 g, 10 mmoles) in dry methanol (60 ml) in the presence of sodium methoxide (20 mmoles), the appropriate phenacyl bromide **4** (10 mmoles) was added. The reaction mixture was stirred at reflux temperature for 0.5 hour. The separated solid was filtered off and recrystallized from the appropriate solvent to give **8** (Table V).

The reaction of compound **3** with *p*-nitrophenacyl bromide in dry acetonitrile at reflux temperature for 16 hours led directly to **8e** in moderate yield (60%).

Reaction of Compound **3** with *p*-Methoxyphenacyl Bromide.

To a solution of 3-hydroxy-2-phenyl-4-thioxo-3,4-dihydroquinazoline **3** (2.54 g, 10 mmoles) in dry dimethylformamide (60 ml), *p*-methoxyphenacyl bromide (**4f**) (2.29 g, 10 mmoles) was added. The reaction mixture was stirred at reflux temperature for 2 hours. The resultant solution was

poured into ice-water and the precipitated solid recrystallized from ethanol to produce 3-hydroxy-2-phenyl-4-(*p*-methoxyphenacylthio)quinazolinium bromide as orange needles in 65% yield, mp 265°; ir (nujol): 1600, 1590, 1460, 1350, 1255, 1220, 1180, 1140, 1020, 850, 770, 700 cm^{-1}; ms: (70 eV) m/e 386 (M^+—HBr—16, 18), 354 (66), 326 (13), 247 (26), 219 (17), 205 (21), 135 (100), 107 (22), 77 (90).

Anal. Calcd. for $C_{23}H_{19}BrN_2O_3S$: C, 57.15; H, 3.96; N, 5.79; S, 6.63. Found: C, 57.32; H, 4.03; N, 6.05; S, 6.50.

To a solution of 3-hydroxy-2-phenyl-4-(*p*-methoxyphenacylthio)quinazolinium bromide (5 mmoles) in dry methanol (50 ml), sodium methoxide (5 mmoles) was added. The reaction mixture was heated under reflux temperature for 7 hours. After cooling, the precipitated yellow solid was filtered off and recrystallized from methanol/chloroform (1:1) to give **8f** as yellow needles in 75% yield, mp 170° (Table V).

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REFERENCES AND NOTES

[1] A. Arques, P. Molina and A. Soler, *Synthesis,* 702 (1980).
[2] P. Molina, A. Arques and M. V. Valcarcel, *ibid.,* 944 (1982).
[3] L. Legrand and N. Lozac'h, *Bull. Soc. Chim. France,* 1400 (1961).
[4] P. B. Talukdar, S. K. Sengupta and A. K. Datta, *Ind. J. Chem. (B),* **15**, 1110 (1977).
[5] L. Legrand and N. Lozac'h, *Bull. Soc. Chim. France,* 618 (1961).
[6] D. Chaigne, J. F. Hemidy, L. Legrand and D. Cornet, *J. Chem. Res. (S),* 198 (1977); D. Chaigne, J. F. Hemidy, L. Legrand and D. Cornet, *ibid.,* 160 (1978).
[7] G. Caillaud and Y. Mollier, *Bull. Soc. Chim. France,* 147 (1972).
[8] S. M. Roberts and H. Suschitzky, *Chem. Commun.,* 893 (1967).
[9] M. Weigele and W. Leimgruber, *Tetrahedron Letters,* 715 (1967).
[10] J.-P. Sauve and N. Lozac'h, *Bull. Soc. Chim. France II,* 427 (1980).