Fused Mesoionic Heterocycles: Synthesis of 1,3,4-Triazolo[3,2-*c*]quinazoline Derivatives

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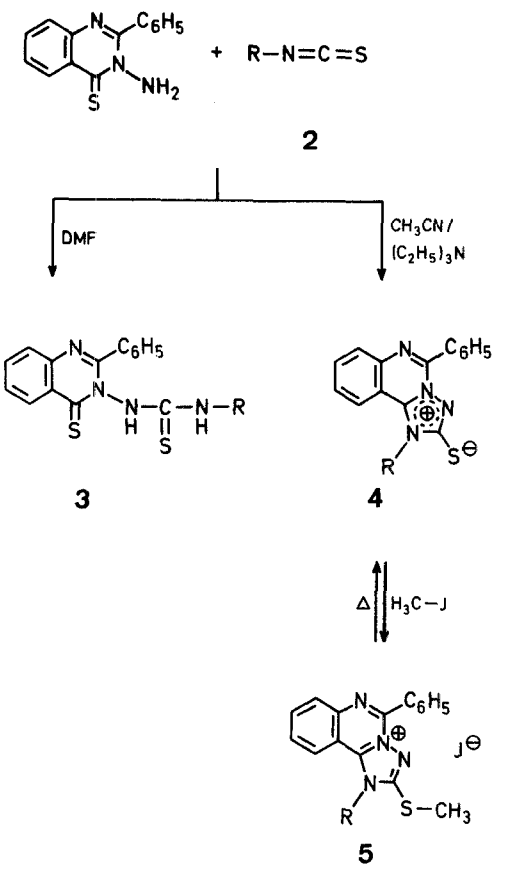
In connection with our investigations on the preparation of fused mesoionic compounds such as 1,3,4-oxadiazolo[3,2-*a*]pyridine[1,2], 1,3,4-thiadiazolo[3,2-*a*]pyridine[2], 1,3,4-triazolo[3,2-*a*]pyridine[3], and 1,2,4-triazolo[4,3-*b*]-1,2,4-triazole[4], we report here a facile synthesis of 1,3,4-triazolo[3,2-*c*]quinazoline derivatives.

No generally useful procedure for the preparation of anhydro-2-mercapto-1,3,4-triazolo[3,2-*c*]quinazolin-4-ium hydroxide derivatives has hitherto been reported; it was only briefly mentioned[5] that anhydro-5-methyl-2-mercapto-1,3,4-thiadiazolo[3,2-*c*]quinazolin-4-ium hydroxide or its corresponding methiodide react with *n*-butylamine or aniline to give the corresponding mesoionic compounds anhydro-2-mercapto-1,3,4-triazolo[3,2-*c*]quinazolin-4-ium hydroxides, the formation of these compounds seems to be strongly dependent on the nature of the substituent on the quinazoline ring.

We report a convenient synthesis of anhydro-1-substituted 5-phenyl-2-mercapto-1,3,4-triazolo[3,2-*c*]quinazolin-4-ium hydroxides **4** by reaction of 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**1**; readily available from 2-phenyl-4-thioxo-1,3-benzothiazine and hydrazine hydrate[6]) with alkyl and aryl isothiocyanates **2**. The *N*-aminoheterocycle **1** reacts with aryl isothiocyanates **2** at reflux temperature in dimethylformamide for 4–7 h, giving *N,N'*-disubstituted thioureas **3** as crystalline solids in moderate to good yields (Table). Compounds **3** do not show in the mass spectra the molecular ion peaks, but show the $M^+ - H_2S$ ion which indicates that these compounds have a strong tendency to expell hydrogen sulfide. When **1** is treated with **2** in dry acetonitrile in the presence of triethylamine at reflux temperature for 24 h, the mesoionic compounds **4** are isolated as crystalline solids in moderate yields (Table). Compounds **4** reacts with methyl iodide to form methiodides **5** which are obtained as stable crystalline solids in excellent yields (Table). When compounds **5** are heated at slightly above their melting points, they are transformed into the mesoionic compounds **4** in near quantitative yields.



Although the *N*-aminoheterocycles 1-amino-4,6-diphenyl-2-thioxo-1,2-dihydropyridine and **1** show structural similarity, both possess the *N*-thioacylhydrazine moiety, they exhibit striking differences in their reactions towards isothiocyanates. The former leads to mesoionic derivatives of the 2-amino-1,3,4-thiadiazolium ring system[2], whereas the latter leads to the isomeric 2-mercapto-1,2,4-triazolium system.

Structural elucidation of **4** and **5** was accomplished on the basis of spectral data and microanalyses. Mass spectra of compounds **4** show the expected molecular ion peaks. The base peak appears at m/e = 205 for the aromatic series (**4**; R = Ar), peaks are also found at $M^+ - 32$ for the loss of sulfur, at $M^+ - 58$ for the loss of NCS, at m/e = 102 and at m/e = 77. In the I.R. spectra the compounds show absorption bands for the thioxo group at ν = 1364–1350 cm^{-1}, which may be compared with the thioxo band shown in bicyclic anhydro-2-mercapto-1,3,4-triazolo[3,2-*a*]pyridinium hydroxides[3].

The simple relationship betwen **4** and **5** was shown by the appearance of the M^+ of **4** as an important ion in the mass spectra of **5**, in addition the base peak for **5** corresponding to the fragment at m/e = 142 (JCH_3). The ^{1}H-N.M.R. spectra of **5** show, among others, a singlet at δ = 2.90 ppm due to the S—CH_3 group.

It has been reported[5] that the reaction of 3-amino-2-methyl-4-thioxo-3,4-dihydroquinazoline with phenyl isothiocyanate in dry ethanol gives the mesoionic anhydro-5-methyl-

Table. Compounds **3**, **4**, and **5** prepared

Compound No.	R	Yield[a] [%]	m.p.[b] [°C] (solvent)	Appearance	Molecular Formula[c]	I.R. (Nujol)[d] ν [cm^{-1}]	1H-N.M.R.[e] δ [ppm]	M.S.[f] m/e (%)
3a	C_6H_5	55	190° (C_2H_5OH)	yellow plates	$C_{21}H_{16}N_4S_2$ (388.5)	3340, 1600, 1540, 1430, 1325, 1230, 950, 770, 750, 740, 690	10.20 (s, 1H); 8.8–7.6 (m, 15H)	354 (22), 322 (19), 296 (8), 219 (14), 205 (100), 104 (15), 103 (15), 102 (14), 77 (33)
3b	4-Br—C_6H_4	60	223–225° (C_2H_5OH)	orange plates	$C_{21}H_{15}BrN_4S_2$ (467.4)	3320, 1600, 1550, 1540, 1490, 1400, 1365, 1230, 1020, 950, 820, 765	10.15 (s, 1H); 9.1–7.4 (m, 14H)	434 (100), 432 (100), 402 (20), 400 (20), 327 (21), 219 (16), 205 (48), 103 (16), 102 (19), 77 (13)
3c	4-Cl—C_6H_4	75	218–220° (C_2H_5OH)	yellow plates	$C_{21}H_{15}ClN_4S_2$ (423.0)	3350, 1605, 1570, 1550, 1500, 1415, 1385, 1100, 960, 830, 770, 745, 700	10.10 (s, 1H); 8.5–7.3 (m, 14H)	390 (22), 388 (68), 358 (7), 356 (18), 361 (9), 237 (6), 205 (100), 102 (23), 77 (43)
3d	4-H_3C—C_6H_4	57	164° (C_2H_5OH)	yellow plates	$C_{22}H_{18}N_4S_2$ (402.5)	3260, 1610, 1590, 1540, 1470, 1370, 1350, 1160, 780, 765, 715, 690	10.20 (s, 1H); 8.9–7.2 (m, 14H); 2.25 (s, 3H)	368 (53), 336 (35), 309 (12), 237 (7), 205 (100), 102 (27), 77 (82)
4a	C_6H_5	59	286–287° ($CHCl_3$)	white needles	$C_{21}H_{14}N_4S$ (354.4)	1613, 1562, 1528, 1480, 1364, 1183, 1157, 775, 707, 696	8.8–7.25 (m, H_{arom})	354 (M^+, 78), 353 (57), 321 (18), 296 (13), 277 (10), 205 (100), 102 (45), 77 (98)
4b	4-Br—C_6H_4	73	273–274° ($CHCl_3$)	white needles	$C_{21}H_{13}BrN_4S$ (433.3)	1619, 1596, 1540, 1489, 1355, 1245, 1075, 826, 764, 696, 628	8.7–7.2 (m, H_{arom})	434 ($M^+ + 2$, 3), 433 (2), 432 (M^+, 3), 431 (2), 402 (5), 401 (5), 400 (5), 399 (5), 376 (3), 374 (3), 205 (100), 157 (19), 155 (19), 102 (36), 77 (40)
4c	4-Cl—C_6H_4	52	284–286° ($CHCl_3$)	yellow needles	$C_{21}H_{13}ClN_4S$ (388.9)	1619, 1596, 1557, 1523, 1398, 1350, 1291, 1262, 1166, 1087, 1019, 843, 764, 701, 633	8.9–7.2 (m, H_{arom})	390 ($M^+ + 2$, 7), 389 (8), 388 (M^+, 19), 387 (22), 358 (5), 357 (7), 356 (15), 355 (18), 332 (3), 330 (8), 277 (4), 205 (100), 102 (29), 77 (55)
4d	4-H_3C—C_6H_4	53	275–277° ($CHCl_3$)	brown needles	$C_{22}H_{16}N_4S$ (368.5)	1613, 1557, 1528, 1364, 1352, 1339, 1296, 1262, 1160, 769, 707, 690	8.8–7.2 (m, 13H), 2.6 (s, 3H)	368 (M^+, 32), 367 (30), 336 (14), 335 (14), 310 (20), 277 (3), 205 (100), 102 (34), 91 (22), 77 (53)
4e	n-C_3H_7	54	225–227° (C_2H_5OH)	white needles	$C_{18}H_{16}N_4S$ (320.4)	1613, 1557, 1534, 1393, 1364, 1115, 764, 703, 692	8.8–7.6 (m, 9H), 4.85 (t, 2H); 2.15 (m, 2H); 1.20 (t, 3H)	320 (M^+, 23), 288 (5), 279 (17), 278 (80), 277 (81), 246 (36), 220 (27), 205 (94), 102 (91), 77 (100)
4f	$C_6H_5CH_2$	53	128–131° ($CHCl_3$)	yellow prisms	$C_{22}H_{16}N_4S$ (368.5)	1613, 1596, 1557, 1517, 1393, 1359, 1347, 1228, 1149, 758, 747, 701	8.8–7.6 (m, 14H); 6.20 (s, 2H)	368 (M^+, 30), 336 (7), 335 (22), 247 (23), 205 (41), 102 (21), 91 (100), 77 (30)

Table (Continued)

5a	C_6H_5	91	286–287° ($CHCl_3$)	white prisms	$C_{22}H_{17}IN_4S$ (496.4)	1625, 1562, 1534, 1279, 775, 707, 690, 622	7.8–6.8 (m, 14H); 2.90 (s, 3H)	354 (33), 353 (30), 322 (12), 321 (16), 296 (12), 277 (5), 205 (80), 142 (100), 127 (61), 102 (46), 77 (95)
5b	4-Br—C_6H_4	88	276–277° ($CHCl_3$)	white prisms	$C_{22}H_{16}BrIN_4S$ (575.3)	1625, 1602, 1568, 1534, 1421, 1279, 1143, 1070, 1010, 826, 764, 701	8.8–7.2 (m, 13H); 2.90 (s, 3H)	434 (13), 433 (14), 432 (13), 431 (12), 401 (3), 399 (3), 294 (13), 205 (49), 142 (100), 127 (49), 102 (19), 77 (22)
5c	4-Cl—C_6H_4	93	279–280° ($CHCl_3$)	white prisms	$C_{22}H_{16}ClIN_4S$ (530.8)	1625, 1562, 1534, 1506, 1274, 1143, 1087, 849, 764, 707, 628	8.6–7.3 (m, 13H); 2.90 (s, 3H)	390 (9), 389 (10), 388 (25), 387 (27), 356 (4), 330 (4), 294 (7), 277 (6), 205 (46), 142 (100), 127 (50), 102 (20), 77 (28)
5d	4-H_3C—C_6H_4	86	278–279° ($CHCl_3$)	white prisms	$C_{23}H_{19}IN_4S$ (510.4)	1625, 1562, 1528, 1279, 1143, 832, 764, 718, 707, 645	8.8–7.4 (m, 13H); 2.90 (s, 3H); 2.65 (s, 3H)	368 (30), 367 (26), 336 (10), 335 (10), 310 (5), 205 (66), 142 (100), 127 (48), 102 (37), 91 (20), 77 (55)
5e	*n*-C_3H_7	85	168–173° (C_2H_5OH)	yellow prisms	$C_{19}H_{19}IN_4S$ (462.4)	1625, 1562, 1534, 1387, 1240, 945, 908, 775, 701, 698, 680	8.6–7.2 (m, 9H); 4.75 (t, 2H); 2.92 (s, 3H); 2.20 (m, 2H); 1.20 (t, 3H)	320 (6), 292 (38), 278 (18), 277 (20), 205 (25), 142 (100), 127 (60), 77 (20)
5f	$C_6H_5CH_2$	90	148–150° (C_2H_5OH)	white prisms	$C_{23}H_{19}IN_4S$ (510.4)	1625, 1523, 1494, 1274, 951, 764, 718, 690	8.7–7.3 (m, 14H); 5.80 (s, 2H); 2.88 (s, 3H)	368 (18), 336 (3), 335 (11), 247 (14), 205 (24), 142 (100), 127 (53), 102 (22), 91 (86), 77 (23)

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] The microanalyses were in good agreement with the calculated values (C ±0.28, H ±0.28, N ±0.26).
[d] Recorded on a Nicolet FT 5DX spectrometer.
[e] Recorded at 60 MHz on a Varian EM-360A spectrometer with TMS as internal standard. For compounds **3** and **5a** DMSO-d_6 was used as solvent while for compounds **4** and **5b–5f** $CDCl_3/CF_3COOH$ was used.
[f] Recorded at 70 eV on a Hewlett-Packard 5993C instrument.

1-phenyl-2-mercapto-1,3,4-triazolo[3,2-*c*]quinazolin-4-ium hydroxide in low yield (15%), but this has remained the sole example of this reaction type and under the same reaction conditions 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline appears to be unreactive. This procedure has limitations in terms of yield and general applicability and so is unsatisfactory from a preparative point of view. The procedure reported here is of considerable utility as a general method for the preparation of this class of mesoionic compounds.

***N,N'*-Disubstituted Thioureas 3; General Procedure:**
To a solution of 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**1**; 0.5 g, 2 mmol) in dry dimethylformamide (10 ml), the appropriate isothiocyanate **2** (4 mmol) is added. The deep red solution is refluxed for 4–7 h. After cooling at room temperature, the mixture is poured into ice/water (20 ml) and the precipitated solid crude recrystallized from the appropriate solvent to give products **3** as crystalline solids (Table).

Anhydro-1-substituted 5-Phenyl-2-mercapto-1,3,4-triazolo[3,2-*c*]quinazolin-4-ium Hydroxides 4; General Procedure:
To a solution of 3-amino-2-phenyl-4-thioxo-3,4-dihydroquinazoline (**1**; 0.5 g, 2 mmol) in dry acetonitrile (15 ml), the appropriate isothiocyanate **2** (4 mmol) and triethylamine (4 mmol) are added. The mixture is heated at reflux for 24 h. After cooling at room temperature, the crude product is separated and recrystallized from the appropriate solvent to give products **4** (Table).

Methiodides 5; General Procedure:
To a solution of **4** (1 mmol) in dichloromethane (10 ml), methyl iodide (2 mmol) is added. After few minutes (15), a yellow precipitated solid separates. The mixture is refluxed for additional 15 min. After cooling, the precipitate is collected by filtration and recrystallized from the appropriate solvent to give methiodides **5** as crystalline solids (Table).

Thermolysis of Methiodides 5; General procedure:
The dry iodide **5** (2 mmol) is heated at a temperature slightly above its melting point under reduced pressure (1 torr) for 30 min. After cooling, the residue is recrystallized from chloroform to give **4** in almost quantitative yields.

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