One-Pot Synthesis of 3-Arylquinazoline-2,4(1*H*,3*H*)-dithiones by the Reaction of 2-Lithiophenyl Isothiocyanates with Aryl Isothiocyanates

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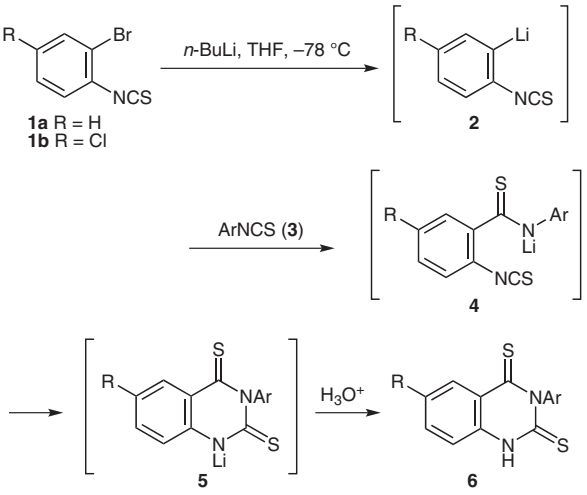
Received 14 February 2011; revised 24 March 2011

Abstract: 3-Arylquinazoline-2,4(1*H*,3*H*)-dithiones were synthesized in satisfactory yields from 2-bromophenyl isothiocyanates in one pot via generation of the corresponding 2-lithiophenyl isothiocyanates by bromine–lithium exchange with butyllithium followed by treatment with aryl isothiocyanates.

Key words: quinazoline-2,4(1*H*,3*H*)-dithiones, 2-lithiophenyl isothiocyanates, 2-bromophenyl isothiocyanates, aryl isothiocyanates, benzothioamides

Although the first synthesis of quinazoline-2,4(1*H*,3*H*)-dithione by the reaction of 2-aminobenzonitrile with carbon disulfide in refluxing pyridine was described by Taylor and co-workers in 1966,[1] there has been but limited attention paid to compounds having this skeleton until the recent reports on the biological evaluation of 3-arylquinazoline-2,4(1*H*,3*H*)-dithiones and related compounds as antimycobacterial agents,[2a] phosphodiesterase 7 inhibitors,[2b] and so on.[3] The synthesis of these compounds was generally based on the treatment of the corresponding 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones with phosphorous pentasulfide[2a] or Lawesson's reagent.[2b] On the other hand, we have demonstrated, in a recent publication, that 2-lithiophenyl isothiocyanates can be generated by the treatment of 2-bromophenyl isothiocyanates with butyllithium and can serve as intermediates for the synthesis of 1,4-dihydro-3,1-benzoxazine-2-thiones through reaction with aldehydes, ketones, or butanolide.[4] As part of our efforts to explore the synthetic utility and potential of these lithium products, we have investigated the possibility of their use in the preparation of quinazoline-2,4(1*H*,3*H*)-dithiones by reacting them with isothiocyanates. In this paper, the results of our studies, which offer a new and efficient route to 3-arylquinazoline-2,4(1*H*,3*H*)-dithiones by the reaction of these lithium products with aryl isothiocyanates, are reported.

The synthesis of 3-arylquinazoline-2,4(1*H*,3*H*)-dithiones **6** from 2-bromophenyl isothiocyanates **1** was conducted as illustrated in Scheme 1. Treatment of **1** with an equimolar amount of butyllithium at –78 °C in THF generated 2-lithiophenyl isothiocyanates **2**, which were allowed to react with aryl isothiocyanates **3** to give the lithium thioamide intermediates **4**. Cyclization of these intermediates gave 3-aryl-1-lithioquinazoline-2,4(1*H*,3*H*)-dithione intermediates **5**, which were protonated by aqueous workup to give the desired products **6**. Yields of these products after purification by recrystallization are summarized in Table 1, which are generally fair-to-good. The structure determination of **6a** was performed by comparison of its ^{1}H and ^{13}C NMR spectra to those reported previously.[2b] Each of the products **6** was isolated by recrystallization and each ^{13}C NMR spectrum uniformly shows signals at ca. δ = 172 and 188 ppm assignable to 2- and 4-thioxo carbons, respectively.



Scheme 1 Preparation of 3-arylquinazoline-2,4(1*H*,3*H*)-dithiones **6**

Our attempt to obtain 3-butylquinazoline-2,4(1*H*,3*H*)-dithione by the reaction of 2-lithiophenyl isothiocyanate (**2a**) with *n*-butyl isothiocyanate was unsuccessful. Instead of the expected product, 3-phenylquinazoline-2,4(1*H*,3*H*)-dithione (**6a**) was obtained in 56% yield based on **1a**. The formation of **6a** may be interpreted as follows. Part of lithiated compound **2a** is protonated probably by proton abstraction from the α-position of *n*-butyl isothiocyanate to give phenyl isothiocyanate (**3a**), which reacts with remaining **2a** to provide **6a**, as shown in Scheme 2.

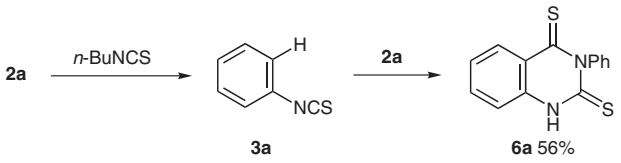
3-Aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones could be expected to be formed by the application of the present reaction using aryl isocyanates in place of aryl isothiocyanates. But, the reaction of 2-lithiophenyl isothiocyanate (**2a**) with phenyl isocyanate only resulted in the formation

SYNTHESIS 2011, No. 10, pp 1526–1528
Advanced online publication: 19.04.2011
DOI: 10.1055/s-0030-1260016; Art ID: F19411SS

Table 1 Preparation of 3-Arylquinazoline-2,4(1*H*,3*H*)-dithiones **6**

Entry	1	Ar in 3	6	Yield (%)[a]
1	**1a**	Ph (**3a**)	**6a**	74
2	**1a**	3-MeC_6H_4 (**3b**)	**6b**	71
3	**1a**	3,5-$Me_2C_6H_3$ (**3c**)	**6c**	72
4	**1a**	2-ClC_6H_4 (**3d**)	**6d**	62
5	**1a**	3-ClC_6H_4 (**3e**)	**6e**	80
6	**1a**	2-BrC_6H_4 (**3f**)	**6f**	58
7	**1a**	3-$MeOC_6H_4$ (**3g**)	**6g**	70
8	**1a**	naphthalen-2-yl (**3h**)	**6h**	64
9	**1b**	Ph (**3a**)	**6i**	63
10	**1b**	2-Br,4-ClC_6H_3 (**3j** = **1b**)	**6j**	61

[a] Isolated yields.



Scheme 2 Attempted synthesis of 3-butylquinazoline-2,4(1*H*,3*H*)-dithione

of intractable mixture of products, from which no more than a trace amount of the desired product could be obtained in a pure form. This result is most likely due to susceptibility of isocyanates to oligomerization under the reaction conditions.

In conclusion, we have demonstrated that the reaction of 2-lithiophenyl isothiocyanates with aryl isothiocyanates provides rapid access to 3-arylquinazoline-2,4(1*H*,3*H*)-dithiones. The present new method may find some value in synthesis, because it is operationally simple and the starting materials are readily available.

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined as KBr disks with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were determined using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz or a JEOL LA400 FT NMR spectrometer operating at 100 MHz. Low-resolution mass spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Wako Gel C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use. All chemicals, excluding 2-bromo-4-chlorophenyl isothiocyanate (**1b**) and 3,5-dimethylphenyl isothiocyanate (**3c**), were commercially available. Compound **1b** was prepared according to the procedure reported previously.[4] Compound **3c**[5] was prepared from 3,5-dimethylphenyl isocyanide[6] according to the procedure employed for the preparation of **1b**.[4]

3-Phenylquinazoline-2,4(1*H*,3*H*)-dithione (6a);[2] Typical Procedure

To a stirred solution of **1a** (0.21 g, 1.0 mmol) in THF (4 mL) at –78 °C was added *n*-BuLi (1.6 M in hexane, 0.03 mL, 1.0 mmol) dropwise. After 1 min, **3a** (0.14 g, 1.0 mmol) was added and the stirring was continued for an additional 10 min at the same temperature before sat. aq NH_4Cl (10 mL) was added. The mixture was warmed to r.t. and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residual solid, which was recrystallized from hexane–$CHCl_3$ to give **6a** as an orange solid; yield: 0.20 g (74%); mp 253–255 °C (Lit.[2b] mp 253–256 °C).

^{1}H and ^{13}C NMR spectral data for this product were identical with those reported previously.[2b]

3-(3-Methylphenyl)quinazoline-2,4(1*H*,3*H*)-dithione (6b)

Yellow solid; mp 176–178 °C (hexane–THF).

IR (KBr): 3158, 1616, 1604, 1371 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.31 (s, 3 H), 6.98–7.01 (m, 2 H), 7.17 (d, *J* = 7.3 Hz, 1 H), 7.32–7.37 (m, 2 H), 7.42 (d, *J* = 7.8 Hz, 1 H), 7.78 (ddd, *J* = 8.3, 7.8, 1.5 Hz, 1 H), 8.32 (d, *J* = 8.3 Hz, 1 H), 13.44 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.9, 116.0, 123.7, 125.3, 125.6, 128.67, 128.69, 129.1, 131.8, 135.3, 135.8, 138.6, 144.1, 172.8, 189.7.

MS: *m*/*z* (%) = 284 ([M$^+$], 100).

Anal. Calcd for $C_{15}H_{12}N_2S_2$: C, 63.35; H, 4.25; N, 9.85. Found: C, 63.18; H, 4.30; N, 9.69.

3-(3,5-Dimethylphenyl)quinazoline-2,4(1*H*,3*H*)-dithione (6c)

Pale-yellow solid; mp 188–189 °C (hexane–THF).

IR (KBr): 3160, 1605, 1368 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.71 (s, 6 H), 6.51 (s, 2 H), 6.83 (s, 1 H), 7.35 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.46 (d, *J* = 8.4 Hz, 1 H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 8.14 (dd, *J* = 8.4, 1.5 Hz, 1 H), 13.32 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.0, 116.7, 118.1, 119.1, 125.5, 125.8, 126.6, 134.0, 138.8, 139.0, 148.7, 172.5, 185.8.

MS: *m*/*z* (%) = 298 ([M$^+$], 100).

Anal. Calcd for $C_{16}H_{14}N_2S_2$: C, 64.39; H, 4.73; N, 9.39. Found: C, 64.29; H, 4.76; N, 9.22.

3-(2-Chlorophenyl)quinazoline-2,4(1*H*,3*H*)-dithione (6d)

Orange solid; mp 239–241 °C (hexane–THF).

IR (KBr): 3161, 1614, 1398 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.33–7.49 (m, 5 H), 7.57 (dd, *J* = 8.8, 1.5 Hz, 1 H), 7.82 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 1 H), 8.32 (dd, *J* = 8.3, 0.9 Hz, 1 H), 13.58 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.2, 123.2, 125.6, 128.4, 129.9, 130.0, 130.8, 130.9, 131.6, 135.3, 136.3, 141.0, 171.9, 188.7.

MS: *m*/*z* (%) = 304 ([M$^+$], 100).

Anal. Calcd for $C_{14}H_9ClN_2S_2$: C, 55.16; H, 2.98; N, 9.19. Found: C, 55.35; H, 2.76; N, 9.05.

3-(3-Chlorophenyl)quinazoline-2,4(1*H*,3*H*)-dithione (6e)

Orange solid; mp 256–258 °C (hexane–THF).

IR (KBr): 3165, 1618, 1603, 1400 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.22 (dd, *J* = 8.4, 1.5 Hz, 1 H), 7.35 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.40–7.45 (m, 3 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.79 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 8.32 (dd, *J* = 8.4, 1.5 Hz, 1 H), 13.50 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 116.0, 123.7, 125.3, 127.7, 128.1, 128.8, 130.8, 131.6, 133.2, 135.3, 135.9, 145.3, 172.6, 189.8.

MS: *m*/*z* (%) = 304 ([M$^+$], 100).

Anal. Calcd for $C_{14}H_9ClN_2S_2$: C, 55.16; H, 2.98; N, 9.19. Found: C, 55.18; H, 3.02; N, 9.25.

3-(2-Bromophenyl)quinazoline-2,4(1*H*,3*H*)-dithione (6f)
Orange solid; mp 250–254 °C (hexane–THF).

IR (KBr): 3161, 1614, 1395 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.31–7.38 (m, 2 H), 7.43–7.45 (m, 2 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.71 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.81 (dd, *J* = 7.8, 7.3 Hz, 1 H), 8.32 (d, *J* = 7.8 Hz, 1 H), 13.57 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.1, 121.8, 123.3 125.5, 128.9, 130.0, 130.9, 131.6, 133.1, 135.3, 136.2, 142.5, 171.9, 188.5.

MS: *m*/*z* (%) = 348 ([M$^+$], 100).

Anal. Calcd for $C_{14}H_9BrN_2S_2$: C, 48.14; H, 2.60; N, 8.02. Found: C, 48.02; H, 2.71; N, 8.04.

3-(3-Methoxyphenyl)quinazoline-2,4(1*H*,3*H*)-dithione (6g)
Orange solid; mp 269–271 °C (hexane–THF).

IR (KBr): 3153, 1620, 1605, 1396 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.73 (s, 3 H), 6.78 (dd, *J* = 7.8, 2.0 Hz, 1 H), 6.82 (t, *J* = 2.0 Hz, 1 H), 6.94 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.37 (dd, *J* = 8.3, 7.8 Hz, 1 H), 7.41 (d, *J* = 8.3 Hz, 1 H), 7.77 (ddd, *J* = 8.3, 7.8, 1.5 Hz, 1 H), 8.31 (d, *J* = 7.8 Hz, 1 H), 13.40 (br s, 1 H)

^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.3, 113.4, 114.6, 116.1, 120.8, 123.8, 125.3, 130.0, 131.8, 135.4, 135.9, 145.2, 160.2, 172.8, 189.6.

MS: *m*/*z* (%) = 300 ([M$^+$], 100).

Anal. Calcd for $C_{15}H_{12}N_2OS_2$: C, 59.97; H, 4.03; N, 9.33. Found: C, 59.85; H, 4.05; N, 9.27.

3-(Naphthalen-2-yl)quinazoline-2,4(1*H*,3*H*)-dithione (6h)
Pale-yellow solid; mp 171–173 °C (hexane–THF).

IR (KBr): 3160, 1614, 1373 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.29–7.60 (m, 5 H), 7.70–7.89 (m, 2 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 8.3 Hz, 1 H), 8.00 (d, *J* = 8.8 Hz, 1 H), 8.33 (dd, *J* = 8.3, 1.0 Hz, 1 H), 13.55 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.1, 123.8, 125.4, 126.1, 126.6, 126.8, 126.9, 127.7, 128.1, 128.9, 131.7, 132.4, 133.5, 135.4, 135.9, 141.7, 173.0, 190.0.

MS: *m*/*z* (%) = 320 ([M$^+$], 100).

Anal. Calcd for $C_{18}H_{12}N_2S_2$: C, 67.47; H, 3.77; N, 8.74. Found: C, 67.21; H, 3.95; N, 8.65.

6-Chloro-3-phenylquinazoline-2,4(1*H*,3*H*)-dithione (6i)
Pale-pink solid; mp 225–230 °C (hexane–$CHCl_3$).

IR (KBr): 3150, 1611, 1387 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.8 Hz, 1 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 7.50–7.60 (m, 4 H), 8.47 (d, *J* = 2.4 Hz, 1 H), 10.87 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.5, 125.4, 128.1, 129.0, 129.9, 132.2, 132.5, 135.5, 135.5, 143.7, 173.2, 188.5.

MS: *m*/*z* (%) = 304 ([M$^+$], 100).

Anal. Calcd for $C_{14}H_9ClN_2S_2$: C, 55.16; H, 2.98; N, 9.19. Found: C, 54.93; H, 3.23; N, 9.03.

3-(2-Bromo-4-chlorophenyl)-6-chloroquinazoline-2,4(1*H*,3*H*)-dithione (6j)
Orange solid; mp 188–190 °C (hexane–THF).

IR (KBr): 3154, 1611, 1386 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.46 (d, *J* = 8.6 Hz, 1 H), 7.49 (d, *J* = 8.6 Hz, 1 H), 7.60 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.88 (dd, *J* = 8.6, 2.3 Hz, 1 H), 7.89 (d, *J* = 2.3 Hz, 1 H), 8.24 (d, *J* = 2.3 Hz, 1 H), 13.51 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 118.6, 122.8, 124.3, 129.3, 129.7, 130.1, 132.2, 132.6, 133.7, 134.2, 136.1, 141.6, 171.7, 187.2.

MS: *m*/*z* (%) = 415 ([M$^+$], 100).

Anal. Calcd for $C_{14}H_7BrCl_2N_2S_2$: C, 40.21; H, 1.69; N, 6.70. Found: C, 40.24; H, 1.75; N, 6.55.

Acknowledgment

This work was partially financial supported by a Grand-in-Aid for Scientific Research (C) 22550035 from Japan Society for the Promotion of Science. The authors thank Mrs. Miyuki Tanmatsu of this university for recording the mass spectra and performing combustion analyses.

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