# Synthesis of 2-(4-Quinazolinyl)ethyl Sulfides *via* Addition of Thiols to 4-Vinylquinazolines



Jack G. Samaritoni* and George E. Babbitt

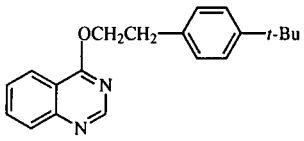
DowElanco Discovery Research, DowElanco, Indianapolis, IN 46268

Received February 25, 1997

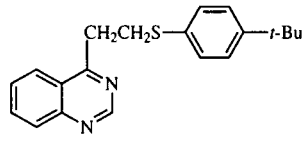
Reaction of vinyl and isopropenyl Grignard reagents with quinazoline results in addition to the 3,4-imine bond to give the 4-alkenyldihydroquinazolines **4** which are conveniently aromatized with potassium ferricyanide to the 4-alkenylquinazolines **5**. Quinazolines **5** undergo addition with thiols under neutral conditions to afford the quinazolinylethyl sulfides **2** in moderate yields.

*J. Heterocyclic Chem.*, **34**, 1263 (1997).

During the course of a research program aimed at evaluating analogs of fenazaquin (**1**) as insect control agents, quinazoline **2a** was targeted for synthesis. Construction of quinazolines alkylated at C-4 is usually accomplished through Bischler's synthesis [1], which involves cyclization of *N*-acyl-*o*-aminoacetophenones with ammonia, or by addition of Grignard reagents to the 4-position of the quinazoline nucleus followed by rearomatization of the dihydroquinazoline intermediate [2]. Application of the latter approach appeared quite attractive since the vinylquinazoline **5a** should be an excellent acceptor and precursor to **2a**. Addition of various nucleophiles to 4-vinylpyridine and 6-vinylguanosines has been well documented in the literature [3,4]; however, the application to vinyldiazines, as well as the syntheses of 4-vinylquinazolines, have not been reported. This paper describes a convenient preparation of 4-vinylquinazolines from commercially available quinazoline and vinylmagnesium bromides and their addition reactions with various thiols.




**1**

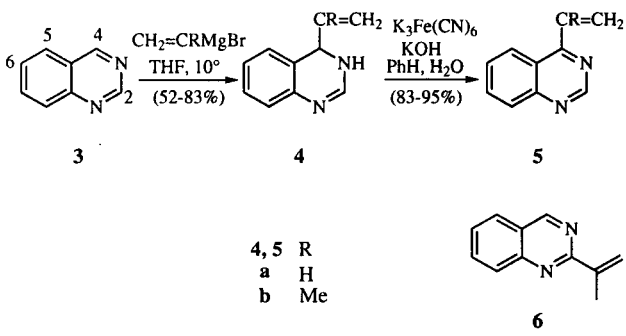



**2a**

Treatment of quinazoline (**3**) at 10° with a slight excess of vinylmagnesium bromide afforded an 83% yield of the dihydroquinazoline **4a** (Scheme 1) as evidenced by mass and proton nmr spectra, the latter exhibiting the characteristic coupling pattern of an allylic system and whose C-2 proton is observed at 7.35 ppm. Oxidation of **4a** was carried out using potassium ferricyanide to give 4-vinylquinazoline (**5a**) in 95% yield. Proton nmr analysis revealed the coupling pattern of a terminal vinyl group as well as the appearance of the C-2 quinazoline proton at 9.32 ppm.

Isopropenylmagnesium bromide was also found to add to C-4 of quinazoline (**3**) to give the dihydro derivative **4b** (Scheme 1), which was then oxidized to the quinazoline **5b**. Proton nmr analysis of the crude reaction mixture

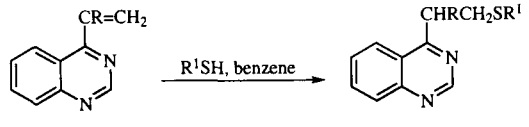
Scheme 1




indicated the presence of the two regioisomers **5b** and **6** in an 11 to 1 ratio in favor of **5b**. The isomers were easily separated by silica gel chromatography and their structural identities were conclusively established from proton nmr (DMSO-$d_6$) nuclear Overhauser enhancement (nOe) difference spectroscopy. Irradiation of H-4 (9.56 ppm) of isomer **6** resulted in enhancement at H-5 (8.11 ppm), indicating the two protons to be within 4.0 Ångstroms [5] and occupying adjacent peri positions in the molecule. Consistent with this result was the observation that irradiation of H-5 produced enhancements at H-4 and H-6. Irradiation of H-2 (9.29 ppm) of **5b** gave no enhancements as expected for such an isolated position, being greater than 4.0 Ångstroms from any neighboring protons.

Treatment of **5a** with 4-*t*-butylthiophenol in benzene afforded a 58% yield of the addition product **2a** (Table 1). Additions to **5** were carried out with a number of thiols as shown and, in general, gave moderate yields of **2** under the neutral conditions employed. Thiophenols **10c** and **10e-f**, required for the preparation of **2c** and **2e-f**, were obtained from the corresponding phenols **7** according to the method of Newman and Karnes [6] as illustrated in Scheme 2. The phenols were first converted to their *O*-arylthiocarbamates **8** which were then thermally rearranged to the isomeric *S*-arylthiocarbamates **9**. Basic hydrolysis then afforded thiols **10** which were immediately used in the addition reactions.

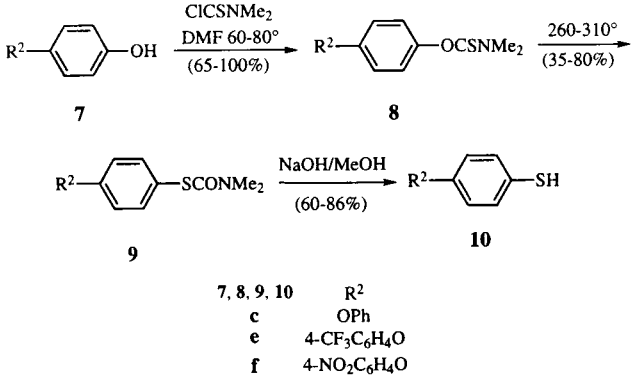
Table 1




5 2a-l

| Product | R | $R^1$ | Yield |
|---|---|---|---|
| **2a** | H | 4-*t*-$BuC_6H_4$ | 58 |
| **2b** | H | 4-$MeOC_6H_4$ | 46 |
| **2c** | H | 4-$PhOC_6H_4$ | 54 |
| **2d** | H | 4-$NO_2C_6H_4$ | 3 |
| **2e** | H | 4-$CF_3C_6H_4OC_6H_4$ | 51 |
| **2f** | H | 4-$NO_2C_6H_4OC_6H_4$ | 53 |
| **2g** | H | 2-$PhOC_6H_4$ | 36 |
| **2h** | H | 5-$CF_3$pyridin-2-yl | 29 |
| **2i** | H | *n*-heptyl | 25 |
| **2j** | Me | 4-*t*-$BuC_6H_4$ | 28 |
| **2k** | Me | 4-$MeOC_6H_4$ | 56 |
| **2l** | Me | 4-$PhOC_6H_4$ | 21 |

Scheme 2




7 8 9 10

| 7, 8, 9, 10 | $R^2$ |
|---|---|
| **c** | OPh |
| **e** | 4-$CF_3C_6H_4O$ |
| **f** | 4-$NO_2C_6H_4O$ |

## EXPERIMENTAL

Melting points were measured in open tubes using a Thomas Hoover Capillary Melting Point apparatus and are uncorrected. All reagents purchased were used without further purification. Solvents were dried using 3Å molecular sieves. Chromatography was performed using 230-400 mesh ASTM Silica Gel 60 from EM Science, Darmstadt, Germany. Proton nmr spectra were obtained on a Varian Gemini 300 spectrometer using deuteriochloroform as solvent and are reported in ppm (δ) downfield from tetramethylsilane as internal reference. Mass spectra were obtained on a Hewlett-Packard Model 5989A mass spectrometer using the electron impact (EI, 70eV) chemical ionization (CI) or fast-atom bombardment (FAB) techniques and are reported as m/z. Microanalyses were performed by Midwest Microlab of Indianapolis.

3,4-Dihydro-4-Vinylquinazoline **4a**

To a solution of 22.53 g (173 mmoles) of quinazoline in 50 ml of dry tetrahydrofuran at 10-15° was added dropwise 190 ml (190 mmoles) of vinylmagnesium bromide in tetrahydrofuran. The solution was then allowed to warm to room temperature and was stirred overnight. The solution was cooled to 10° and was treated dropwise with saturated aqueous ammonium chloride (*ca.* 200 ml). The mixture was poured into ice-water (final volume *ca.* 1400 ml) and was extracted twice with ether. The combined extracts were washed once with brine and were dried over magnesium sulfate. Concentration gave 22.8 g (84%) of crude **4a** as a tan solid which resisted attempts at purification by recrystallization; $^1$H nmr: δ 5.18 (m, 3H, $H_4$ and CH=C$H_2$), 5.87 (br s, 1H, N*H*), 6.03 (m, 1H, C*H*=$CH_2$), 6.95 (d, 1H, J = 7.7 Hz), 7.00 (d, 1H, J = 8.0 Hz), 7.05 (m, 1H), 7.19 (m, 1H), 7.35 (s, 1H, $H_2$); ms: (EI) m/z 158 ($M^+$, 24), 157 (19), 146 (100), 131 (49), 118 (36).

4-Vinylquinazoline (**5a**).

To a mixture of 3.03 g (54.3 mmoles) of potassium hydroxide and 13.3 g (40.2 mmoles) of potassium ferricyanide in 15-20 ml of water was added dropwise over a ten minute period a solution of 2.7 g (17 mmoles) of the dihydroquinazoline **4a** in 60 ml of benzene. The mixture was vigorously stirred mechanically for one hour, was then diluted with water/benzene, and the layers were separated. The aqueous phase was extracted once with benzene and the combined extracts were washed with brine and were dried (magnesium sulfate). Concentration gave 2.6 g (98%) of **5a** as an amber oil; $^1$H nmr: δ 5.94 (dd, 1H, $J_{cis}$ = 10.7 Hz and $J_{gem}$ = 1.8 Hz, CH=C$H_2$), 6.87 (dd, 1H, $J_{trans}$ = 16.9 Hz and $J_{gem}$ = 1.8 Hz, CH=C$H_2$), 7.63 (dd, 1H, $J_{trans}$ = 16.9 Hz and $J_{cis}$ = 10.7 Hz, C*H*=$CH_2$), 7.68 (m, 1H), 7.93 (m, 1H), 8.08 (d, 1H, J = 8.5 Hz), 8.24 (d, 1H, J = 8.1 Hz), 9.32 (s, 1H, $H_2$); ms: (EI) m/z 156 ($M^+$, 77), 155 (100). A small sample was purified by silica gel chromatography using dichloromethane/ethyl acetate eluants to give the microanalytical data below.

*Anal.* Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.61; H, 5.23; N, 17.60.

3,4-Dihydro-4-isopropenylquinazoline (**4b**).

To 1.27 g (52.3 mg-atoms) of magnesium powder under 20 ml of dry tetrahydrofuran was added a trace of iodine/dibromoethane and approximately 0.25 ml of 2-bromopropene. The mixture was heated to 45° resulting in color discharge (brown to colorless) and then a solution of 6.32 g (52.3 mmoles) of 2-bromopropene in 5 ml of tetrahydrofuran was added at a rate which kept the temperature at 50-60°. After addition was complete, the contents were heated at reflux for one hour and were then allowed to cool. The suspension was then added dropwise to a solution of 6.81 g (52.3 mmoles) of quinazoline in 25 ml of tetrahydrofuran at 5-10°. The mixture was allowed to warm to room temperature and was stirred overnight. Saturated ammonium chloride was added to the mixture (60 ml) which was then poured onto cold ammonium chloride solution. The mixture was extracted once with ether, and the extract was washed with brine and was dried (magnesium sulfate). Concentration gave 6.3 g of a mixture consisting of 4.6 g (52%, 69% based on converted starting material) of **4b** and 1.7 g of unreacted quinazoline as determined by proton nmr analysis; $^1$H nmr: δ 1.73 (s, 3H, $CH_3$), 4.25 (br s, 1H, N*H*), 4.82 (m, 1H, $H_4$), 4.98 (s, 1H, =$CH_2$), 5.25 (s, 1H, =$CH_2$), 6.90 (m, 1H), 7.02 (m, 2H), 7.18 (m, 1H), 7.27 (s, 1H, $H_2$); ms: (CI) m/z 173 ($M+1^+$, 31), 171

(23), 131 (100). No attempt was made to purify this material but it was used immediately for rearomatization.

4-Isopropenylquinazoline (**5b**).

To a mixture of 21.4 g (65.0 mmoles) of potassium ferricyanide and 4.9 g (87 mmoles) of potassium hydroxide in 35 ml of water vigorously stirred was added dropwise a solution of 6.1 g (26 mmoles) of the dihydroquinazoline **4b** (73% by weight) in 60 ml of benzene (**exotherm**! 25-39°). After one hour, water and benzene were added and the layers were separated. The organic layer was washed once with brine and was dried (magnesium sulfate). Concentration gave 5.05 g of an amber oil consisting of 68% by weight of **5b** representing a 78% yield and 6% by weight of **6** as determined by proton nmr analysis. A small portion was purified by silica gel chromatography using dichloromethane/ethyl acetate eluants. Compound **5b** was obtained as a liquid; $^1$H nmr: δ 2.33 (s, 3H, $CH_3$), 5.38 (bs, 1H, $=CH_2$), 5.75 (m, 1H, $=CH_2$), 7.62 (m, 1H) 7.90 (m, 1H), 8.06 (d, 1H, J = 8.5 Hz), 8.26 (d, 1H, J = 8.3 Hz), 9.29 (s, 1H, $H_2$); ms: (EI) m/z 170 ($M^+$, 61), 169 (100), 155 (48).

*Anal.* Calcd. for $C_{11}H_{10}N_2$: C, 77.61; H, 5.92; N, 16.46. Found: C, 77.29; H, 6.04; N, 16.31.

2-Isopropenylquinazoline (**6**).

This compound was obtained as a tan solid, mp 53-59°; $^1$H nmr: δ 2.37 (s, 3H, $CH_3$), 5.65 (bs, 1H, $=CH_2$), 6.59 (br s, 1H, $=CH_2$), 7.59 (m, 1H) 7.87 (m, 2H), 8.01 (d, 1H, J = 8.3 Hz), 9.35 (s, 1H, $H_4$). ms: (EI) m/z 170 ($M^+$, 58), 169 (100), 51 (78).

*Anal.* Calcd. for $C_{11}H_{10}N_2$: C, 77.61; H, 5.92. Found: C, 77.42; H, 6.28.

General Procedure for the Reaction of Thiols with 4-Vinylquinazolines **4a** and **4b**. Preparation of **2a-l**.

Equimolar quantities of the 4-vinylquinazoline and the thiol in benzene (*ca.* 0.25 *M* each) were stirred at room temperature overnight. The solution was then diluted with benzene, washed twice with 1.0 *N* sodium hydroxide, once with brine and was dried (magnesium sulfate). Concentration gave oils which were chromatographed on silica gel. Compound **2d** precipitated from the reaction solution (benzene) and was recrystallized twice from chloroform.

4-*t*-Butylphenyl 2-(4-Quinazolinyl)ethyl Sulfide (**2a**).

This compound was obtained as a pale yellow solid, mp 95-98°; $^1$H nmr: δ 1.31 (s, 9H, *t*-Bu), 3.50 (t, 2H, J = 8.3 Hz, $CH_2CH_2$), 3.60 (t, 2H, J = 8.3 Hz, $CH_2CH_2$), 7.36 (s, 4H, arom), 7.62 (m, 1H, hetarom), 7.90 (m, 1H, hetarom), 8.04 (m, 2H, hetarom), 9.24 (s, 1H, $H_2$); ms: (FAB) m/z (%) 323 ($M+1^+$, 93), 157 (100).

*Anal.* Calcd. for $C_{20}H_{22}N_2S$: C, 74.49; H, 6.87; N, 8.69; S, 9.94. Found: C, 74.57; H, 6.90; N, 8.73; S, 9.87.

4-Methoxyphenyl 2-(4-Quinazolinyl)ethyl Sulfide (**2b**).

This compound was obtained as an amber oil; $^1$H nmr: δ 3.39 (t, 2H, J = 7.9 Hz, $CH_2CH_2$), 3.53 (t, 2H, J = 7.9 Hz, $CH_2CH_2$), 3.79 (s, 3H, $OCH_3$), 6.84 (d, 2H, J = 8.6 Hz, arom), 7.39 (d, 2H, J = 8.6 Hz, arom), 7.59 (m, 1H, hetarom), 7.84 (m, 1H, hetarom), 7.88 (d, 1H, J = 8.9 Hz, hetarom), 8.02 (d, 1H, J = 8.6 Hz, hetarom), 9.20 (s, 1H, $H_2$); ms: (EI) m/z (%) 296 ($M^+$, 15), 157 (100).

*Anal.* Calcd. for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45; S, 10.82. Found: C, 68.79; H, 5.31; N, 9.44; S, 10.65.

4-Phenoxyphenyl 2-(4-Quinazolinyl)ethyl Sulfide (**2c**).

This compound was obtained as an oil; $^1$H nmr: δ 3.47 (t, 2H, J = 7.0 Hz, $CH_2CH_2$), 3.59 (t, 2H, J = 7.3 Hz, $CH_2CH_2$), 6.92 (d, 2H, J = 8.6 Hz, arom), 7.00 (d, 2H, J = 8.0 Hz, arom), 7.12 (m, 1H, arom), 7.33 (d, 2H, J = 8.0 Hz, arom), 7.40 (d, 2H, J = 8.6 Hz, arom), 7.63 (m, 1H, hetarom), 7.90 (m, 1H, hetarom), 8.02 (d, 1H, J = 7.6 Hz, hetarom), 8.06 (d, 1H, J = 9.2 Hz, hetarom), 9.22 (s, 1H, hetarom); ms: (EI) m/z (%) 358 ($M^+$, 13), 157 (100).

*Anal.* Calcd. for $C_{22}H_{18}N_2OS$: C, 73.71; H, 5.06; N, 7.82; S, 8.95. Found: C, 73.76; H, 5.18; N, 7.90; S, 8.76.

4-Nitrophenyl 2-(4-Quinazolinyl)ethyl Sulfide (**2d**).

This compound was obtained as a crystalline solid, mp 150-151.5° (chloroform); $^1$H nmr: δ 3.67 (s, 4H, $CH_2CH_2$), 7.42 (d, 2H, J = 10.2 Hz, arom), 7.68 (m, 1H, hetarom), 7.92 (m, 1H, hetarom), 8.03-8.12 (m, 2H, hetarom), 8.15 (d, 2H, J = 10.5 Hz, arom), 9.28 (s, 1H, $H_2$); ms: (FAB) m/z (%) 312 ($M+1^+$, 12), 119 (100).

*Anal.* Calcd. for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50; S, 10.30. Found: C, 61.58; H, 4.17; N, 13.35; S, 10.06.

4-(4'-Trifluoromethylphenoxy)phenyl 2-(4-Quinazolinyl)ethyl Sulfide (**2e**).

This compound was obtained as a solid, mp 98-99°; $^1$H nmr: δ 3.53 (t, 2H, J = 7.8 Hz, $CH_2CH_2$), 3.65 (t, 2H, J = 7.6 Hz, $CH_2CH_2$), 6.98 (d, 2H, J = 8.6 Hz, arom), 7.06 (d, 2H, J = 8.6 Hz, arom), 7.43 (d, 2H, J = 8.6 Hz, arom), 7.59 (d, 2H, J = 8.3 Hz, arom), 7.67 (m, 1H, hetarom), 7.94 (m, 1H, hetarom), 8.08 (m, 2H, hetarom), 9.24 (s, 1H, $H_2$); ms: (EI) m/z (%) 426 ($M^+$, 0.5), 43 (100).

*Anal.* Calcd. for $C_{23}H_{17}F_3N_2OS$: C, 64.77; H, 4.02; N, 6.57. Found: C, 64.66; H, 4.12; N, 6.62.

4-(4'-Nitrophenoxy)phenyl 2-(4-Quinazolinyl)ethyl Sulfide (**2f**).

This compound was obtained as a yellow soild, mp 64-68°; $^1$H nmr: δ 3.55 (m, 2H, $CH_2CH_2$), 3.65 (m, 2H, $CH_2CH_2$), 7.02 (d, 2H, arom), 7.04 (d, 2H, arom), 7.45 (d, 2H, J = 8.0 Hz, arom), 7.65 (m, 1H, hetarom), 7.92 (m, 1H, hetarom), 8.06 (m, 2H, hetarom), 8.22 (d, 2H, J = 9.8 Hz, arom), 9.24 (s, 1H, hetarom); ms: (EI) m/z (%) 403 ($M^+$, 0.8), 155 (100).

*Anal.* Calcd. for $C_{22}H_{17}N_3O_3S$: C, 65.49; H, 4.25; N, 10.41. Found: C, 65.58; H, 4.27; N, 10.55.

2-Phenoxyphenyl 2-(4-Quinazolinyl)ethyl Sulfide (**2g**).

This compound was obtained as a light tan solid, mp 86-88°; $^1$H nmr: δ 3.55 (t, 2H, J = 7.5 Hz, $CH_2CH_2$), 3.65 (t, 2H, J = 7.8 Hz, $CH_2CH_2$), 6.94-7.49 (m, 9H, arom), 7.63 (m, 1H, hetarom), 7.92 (m, 1H, hetarom), 8.06 (m, 2H, hetarom), 9.22 (s, 1H, $H_2$); ms: (EI) m/z (%) 358 ($M^+$, 0.7), 157 (100).

*Anal.* Calcd. for $C_{22}H_{18}N_2OS$: C, 73.71; H, 5.06; N, 7.82. Found: C, 73.58; H, 4.96; N, 7.74.

5-Trifluoromethyl-2-pyridinyl 2-(4-Quinazolinyl)ethyl Sulfide (**2h**).

This compound was obtained as a solid, mp 110-113°; $^1$H nmr: δ 3.77 (br s, 4H, $CH_2CH_2$), 7.29 (d, 1H, pyr $H_3$), 7.65 (m, 2H, pyr $H_4$ and Quin H) 7.92 (m, 1H, Quin H), 8.08 (d, 1H, J = 8.4 Hz, Quin H), 8.26 (d, 1H, J = 8.4 Hz, Quin H), 8.71 (s, 1H, pyr $H_6$), 9.26 (s, 1H, Quin $H_2$); ms: (EI) m/z (%) 335 ($M^+$, 0.1), 157 (100).

*Anal.* Calcd. for $C_{16}H_{12}F_3N_3S$: C, 57.30; H, 3.61; N, 12.53. Found: C, 57.26; H, 3.55; N, 12.43.

*n*-Heptyl 2-(4-Quinazolinyl)ethyl Sulfide (**2i**).

This compound was obtained as a pale yellow liquid; $^1$H nmr: δ 0.93 (t, 3H, J = 6.5 Hz, $CH_3$), 1.22-1.43 (m, 8H, $(CH_2)_4$), 1.62 (m, 2H, $SCH_2CH_2CH_2$), 2.62 (t, 2H, J = 6.5 Hz, $SCH_2CH_2CH_2$), 3.11 (t, 2H, J = 7.5 Hz, $SCH_2CH_2$), 3.59 (t, 2H, J = 7.2 Hz, $SCH_2CH_2$), 7.67 (m, 1H, hetarom), 7.91 (m, 1H, hetarom), 8.06 (d, 1H, J = 9.1 Hz, hetarom), 8.15 (d, 1H, J = 9.1 Hz), 9.25 (s, 1H, $H_2$); ms: (FAB) m/z 289 ($M+1^+$, 100), 157 (60).

*Anal.* Calcd. for$C_{17}H_{24}N_2S$: C, 70.78; H, 8.39; N, 9.71; S, 11.11. Found: C, 70.67; H, 8.39; N, 9.67; S, 11.15.

4-*t*-Butylphenyl 2-(4-Quinazolinyl)propyl Sulfide (**2j**).

This compound was obtained as a pale yellow oil; $^1$H nmr: δ 1.31 (s, 9H, *t*-Bu), 1.51 (d, 3H, $CH_3$, J = 6.8 Hz), 3.26 (dd, 1H, $CH_2$, $J_{vic}$ = 7.7 Hz, $J_{gem}$ = 14.2 Hz), 3.59 (dd, 1H, $CH_2$, $J_{vic}$ = 7.2 Hz, $J_{gem}$ = 13.1 Hz), 4.00 (m, 1H, CH), 7.25 ($A_2B_2$, 4H, arom), 7.56 (m, 1H), 7.87 (m, 1H), 7.92 (d, 1H, J = 8.1 Hz), 8.04 (d, 1H, J = 8.1 Hz), 9.24 (s, 1H, $H_2$); ms: (EI) m/z (%) 336 ($M^+$, 0.4), 171 (100).

*Anal.* Calcd. for $C_{21}H_{24}N_2S$: C, 74.95; H, 7.19; N, 8.33. Found: C, 74.86; H, 7.28; N, 8.37.

4-Methoxyphenyl 2-(4-Quinazolinyl)propyl Sulfide (**2k**).

This compound was obtained as a pale yellow oil; $^1$H nmr: δ 1.48 (d, 3H, $CH_3$, J = 6.8 Hz), 3.17 (dd, 1H, $CH_2$, $J_{vic}$ = 7.1 Hz, $J_{gem}$ = 13.6 Hz), 3.54 (dd, 1H, $CH_2$, $J_{vic}$ = 7.5 Hz, $J_{gem}$ = 13.0 Hz), 3.83 (s, 3H, $OCH_3$) 3.96 (m, 1H, CH), 6.81 (d, H, J = 8.3 Hz, arom), 7.25 (d, 2H, J = 8.3 Hz, arom), 7.54 (m, 1H, hetarom), 7.85 (m, 1H, hetarom), 7.90 (d, 1H, J = 8.9 Hz, hetarom), 8.04 (d, 1H, J = 8.9 Hz, hetarom), 9.21 (s, 1H, $H_2$); ms: (EI) m/z (%) 310 ($M^+$, 2), 171 (100).

*Anal.* Calcd. for $C_{18}H_{18}N_2OS$: C, 69.64; H, 5.84; N, 9.03. Found: C, 69.42; H, 5.89; N, 8.99.

4-Phenoxyphenyl 2-(4-Quinazolinyl)propyl Sulfide (**2l**).

This compound was obtained as a pale yellow oil; $^1$H nmr: δ 1.50 (d, 3H, $CH_3$, J = 7.8 Hz), 3.24 (dd, 1H, $CH_2$, $J_{vic}$ = 6.7 Hz, $J_{gem}$ = 13.2 Hz), 3.59 (dd, 1H, $CH_2$, $J_{vic}$ = 7.3 Hz, $J_{gem}$ = 13.2 Hz), 4.02 (m, 1H, CH), 6.89 (d, 2H, J = 8.8 Hz, arom), 7.03 (d, 2H, J = 8.5 Hz, arom), 7.13 (m, 1H, arom), 7.26 (d, 2H, J = 8.8 Hz, arom), 7.36 (m, 2H, arom), 7.60 (m, 1H, hetarom), 7.88 (m, 1H, hetarom), 7.96 (d, 1H, J = 8.3 Hz, hetarom), 8.05 (d, 1H, J = 8.3 Hz, hetarom), 9.26 (s, 1H, $H_2$); ms: (EI) m/z (%) 372 ($M^+$, 1), 171 (100).

*Anal.* Calcd. for $C_{23}H_{20}N_2OS$: C, 74.16; H, 5.41; N, 7.52. Found: C, 74.01; H, 5.26; N, 7.49.

*N,N*-Dimethyl-*O*-[4-(4'-nitrophenoxy)phenyl]thiocarbamate (**8f**).

To a suspension at 0-10° of 0.75 g (18.7 mmoles) of 60% sodium hydride/mineral oil dispersion in 15 ml of dry dimethylformamide was added dropwise a solution of 3.93 g (17.0 mmoles) of 4-(4'-nitrophenoxy)phenol (**7f**) in 10 ml of dimethylformamide. After 0.5 hour a solution of 2.79 g (22.6 mmoles) of *N,N*-dimethylthiocarbamoyl chloride (purified by distillation) in 10 ml of dimethylformamide was added. The mixture was then heated at 80-90° for three hours, and was then allowed to cool. The mixture was poured into 400 ml of ice-water, and the precipitate was collected, air dried, dissolved in dichloromethane and dried over magnesium sulfate. Concentration gave a solid which was triturated under heptane to remove the mineral oil giving 5.4 g (100%) of **8f**. An analytical sample was obtained by recrystallization from ethyl acetate: mp 146-149.5°; $^1$H nmr: δ 3.38 (s, 3H, $N(CH_3)_2$), 3.48 (s, 3H, $N(CH_3)_2$), 7.06 (d, 2H, J = 9.0 Hz, arom), 7.12 (m, 4H, arom), 8.20 (d, 2H, J = 9.6 Hz, arom); ms: (EI) m/z (%) 318 ($M^+$, 4), 72 (100).

*Anal.* Calcd. for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.49; H, 4.39; N, 8.74.

*N,N*-Dimethyl-*S*-[4-(4'-trifluoromethylphenoxy)phenyl]thiocarbamate (**9e**).

A solution of 0.80 g of the thiocarbamate **8e** in 3 ml of dry xylenes was heated in a heavy-walled glass vial fitted with a Teflon screw cap at 265-280° for approximately eleven hours. The xylenes were removed *in vacuo* and the residue was chromatographed on silica gel using dichloromethane as the eluant to afford 640 mg (77% from phenol **7e**) of **9e** as an off-white solid, mp 79-81°; $^1$H nmr: δ 3.05 (br s, 6H, $N(CH_3)_2$), 7.05 (d, 2H, J = 8.4 Hz, arom), 7.11 (d, 2H, J = 9.2 Hz, arom), 7.48 (d, 2H, J = 9.2 Hz, arom), 7.59 (d, 2H, J = 8.6 Hz, arom); ms: (EI) m/z (%) 341 ($M^+$, 5), 72 (100).

*Anal.* Calcd. for $C_{16}H_{14}F_3NO_2S$: C, 56.29; H, 4.13; N, 4.10. Found: C, 56.50; H, 4.08; N, 4.16.

4-(4'-Trifluoromethylphenoxy)benzenethiol (**10e**).

A solution of 0.635 g (1.86 mmoles) of the thiocarbamate **9e** and 1.95 ml (3.91 mmoles) of 2.0 *N* sodium hydroxide in 5 ml of methanol was purged of oxygen with a subsurface stream of nitrogen, and was then heated at reflux for five hours. The solution was concentrated, and the residue was taken up in water and a few ml of 1.0 *N* sodium hydroxide. The aqueous phase was washed once with ether/heptane and once with benzene, was then made acidic to *p*H 1 with 2.0 *N* hydrochloric acid, and was extracted once with ether. The extract was washed with brine, was dried (magnesium sulfate), and was concentrated to afford 0.30 g (60%) of **10e**; ms: (EI) m/z (%) 270 ($M^+$, 51), 69 (100). This material was immediately used without further purification for addition to 4-vinylquinazoline **5a**.

## REFERENCES AND NOTES

[1] A. Bischler, *Ber. Deut. Chem. Ges.*, **24**, 506 (1891).

[2] W. L. F. Armarego, The Chemistry of Heterocyclic Compounds, Vol **24**, Part I, D. J. Brown, ed, Interscience, New York, 1967, pp 35-36.

[3] A. R. Katritsky, I. Takahashi and C. M. Marson, *J. Org. Chem.*, **51**, 4914 (1986).

[4] F. Nagatsugi, K. Uemura, S. Nakashima, M. Maeda and S. Sasaki, *Tetrahedron Letters*, **36**, 421 (1995).

[5] F. A. Bovey, Nuclear Magnetic Resonance, Second Edition, Academic Press, New York, 1988, p 345.

[6] M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).