Reaction of 2-Quinolyl Thiocyanate with C-Nucleophiles

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2-Quinolyl thiocyanate (2) was found to react with C-nucleophiles, *i.e.*, phenylacetonitrile, *p*-chlorophenylacetonitrile, *p*-cyanophenylacetonitrile, *p*-methoxyphenylacetonitrile, ethyl cyanoacetate, and malononitrile, in two ways, depending on the nature of the reagent. The more reactive phenylacetonitrile carbanions attacked at the less reactive sulfur atom, which is less subject to steric effect compared with the 2-position carbon of 2, to give the corresponding sulfides (α-(2-quinolylthio)phenyl- (8), α-(2-quinolylthio)-4-chlorophenyl- (9), α-(2-quinolylthio)-4-cyanophenyl- (10), and α-(2-quinolylthio)-4-methoxyphenylacetonitrile (11)). The less reactive ethyl cyanoacetate and malononitrile carbanions attacked at the more reactive 2-position carbon of 2 to afford the corresponding ipso-substitution products (α-cyano-2-quinolineacetate (4) and 2-quinolinemalononitrile (7)). However, in the reaction of diethyl malonate carbanion, diethyl 2-quinolinemalonate (12) was not obtained, presumably for steric reasons.

Keywords 2-quinolyl thiocyanate; carbanion; active methylene compound; sulfur attack; ipso-substitution; 2-iodoquinoline

We have previously reported that the reaction of 2-quinoxalinyl thiocyanate (**1**) with nucleophiles results in three types of reactions depending upon the nature of the reagent used.[1] For example, **1** reacts with hydroxide ion (being hard) to give a thiol, Grignard reagent (being soft) to give a sulfide, and amine (being relatively hard) to afford an amine derivative.

Our previous paper[1] on the reaction of **1** with ethyl cyanoacetate is the only report on the reaction of *N*-heterocyclic thiocyanates with C-nucleophiles. In order to extend the above work, we investigated the reaction of 2-quinolyl thiocyanate (**2**) with several C-nucleophiles (diethyl malonate, ethyl cyanoacetate, malononitrile, phenylacetonitrile, *p*-chlorophenylacetonitrile, *p*-cyanophenylacetonitrile, and *p*-methoxyphenylacetonitrile). The results are presented here.

Compound **2** possesses three reaction sites for nucleophilic attack, *i.e.*, the ring-carbon linked to the thiocyanato group (2-position carbon) (site a), the sulfur atom (site b), and the cyano carbon (site c) (Fig. 1). In this study, we found that the attack of C-nucleophiles on **2** takes place at sites a and b, but not at site c.

The starting compound **2** was prepared from 2-iodo- (**3**) or 2-chloroquinoline by treatment with potassium thiocyanate in acetic acid.

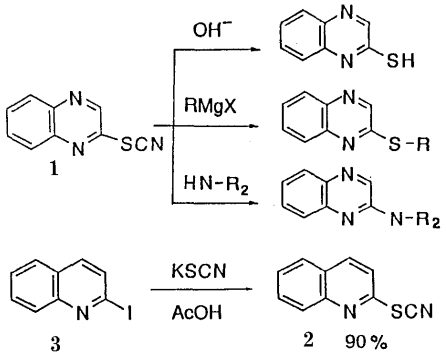


Chart 1

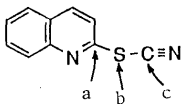


Fig. 1. Three Possible Sites for the Reaction of **2** with Nucleophiles

The reaction of **2** with C-nucleophiles was carried out in the presence of sodium hydride in hexamethylphosphoramide (HMPA) at room temperature under a nitrogen atmosphere. Ethyl cyanoacetate carbanion attacked at the 2-position carbon (site a) to give mainly α-cyano-2-quinolineacetate (**4**) in 52% yield, as reported[1] for **1**, together with some by-products, di-2,2′-quinolyl disulfide (**5**) and 2-quinolinethiol (**6**). Owing to the lower reactivity of the 2-position of **2** compared with that of **1**, the competitive reaction with sodium hydride may have occurred to give these by-products. The reaction with malononitrile carbanion afforded the corresponding 2-quinolinemalononitrile (**7**) in 71% yield with **5** and **6**. Compounds **4** and **7** are ipso-substitution products. Phenylacetonitrile carbanions (phenyl-, *p*-chlorophenyl-, *p*-cyanophenyl-, and *p*-methoxyphenylacetonitrile carbanion) attacked at the sulfur (site b) of **2** to give the corresponding sulfides; α-(2-quinolylthio)phenyl- (**8**, 79%), α-(2-quinolylthio)-4-chlorophenyl- (**9**, 88%), α-(2-quinolylthio)-4-cyanophenyl- (**10**, 80%), and α-(2-quinolylthio)-4-methoxyphenylacetonitrile (**11**, 31%). In the reaction of *p*-methoxyphenylacetonitrile, **5** and **6** were obtained as by-products with **11**. *p*-Methoxyphenylacetonitrile carbanion may react slowly with **2**, owing to the electron-releasing effect of the

TABLE I. Elemental Analysis Data for **2**, **5**, **18** and **8**—**11**

Compd.	mp (°C)	Appearance (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)			
				C	H	N	S
2	74— 75	Colorless needles (Petr. benzin)	$C_{10}H_6N_2S$	64.49 (64.50)	3.25 (3.28)	15.05 (15.03)	17.21 (17.07)
5	140—142	Colorless scales (Petr. benzin)	$C_{18}H_{12}N_2S_2$	67.47 (67.60)	3.78 (3.70)	8.74 (8.74)	20.01 (19.73)
18	186—188	Colorless needles (Petr. benzin)	$C_{18}H_{12}N_2S$	74.97 (74.65)	4.19 (4.20)	9.71 (9.68)	11.12 (10.93)
8	89— 90	Colorless needles (Petr. benzin)	$C_{17}H_{12}N_2S$	73.88 (74.09)	4.37 (4.41)	10.14 (10.20)	11.60 (11.67)
9	124—125	Colorless needles (Petr. benzin)	$C_{17}H_{11}ClN_2S$	65.69 (65.86)	3.57 (3.58)	9.01 (8.82)	10.32 (10.25)
10	115—116	Colorless needles (Petr. benzin)	$C_{18}H_{11}N_3S$	71.73 (71.86)	3.68 (3.69)	13.95 (13.94)	10.64 (10.74)
11	108—109	Colorless prisms (Petr. benzin)	$C_{18}H_{12}N_2O$	70.56 (70.67)	4.61 (4.63)	9.15 (9.10)	10.46 (10.30)

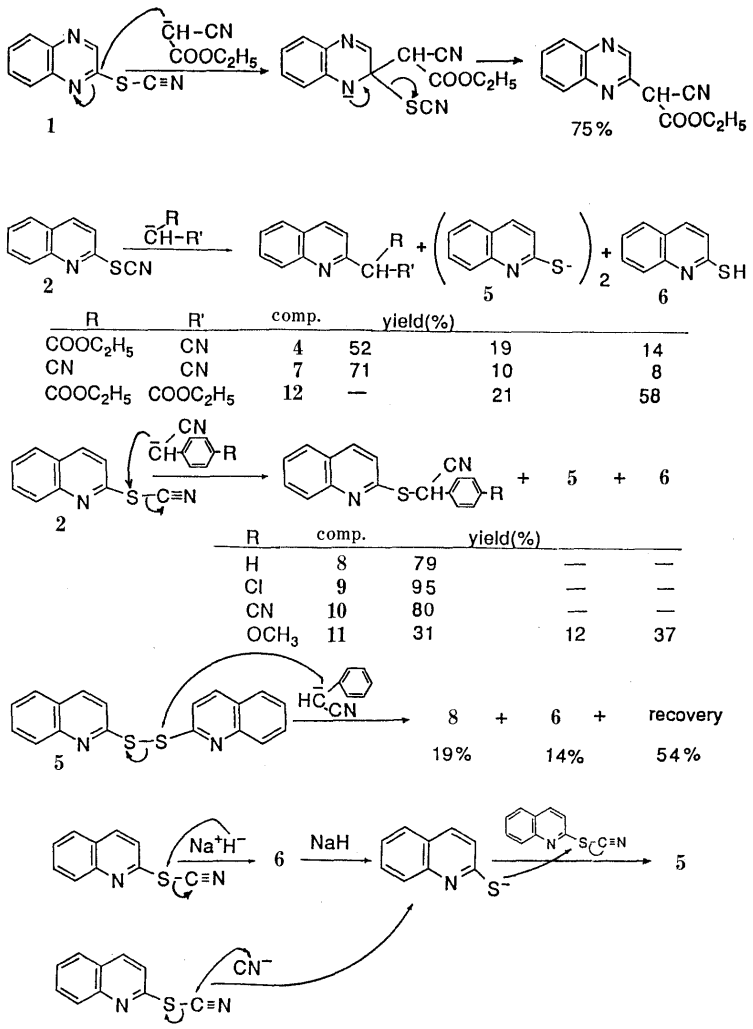
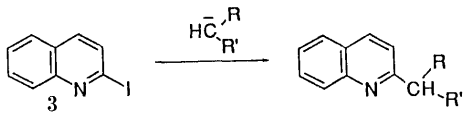


Chart 2

TABLE II. IR and ^{1}H-NMR Spectral Data for **2**, **5**, **18** and **9**—**11**

Compound	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) ppm C^{5-8}H, Ph-H	C^4-H	C^3-H	CH	OCH_3
2	2152 (SCN)	8.05—7.30 (4H, m)	8.13 (1H, d, J=9 Hz)	7.55 (1H, d, J=9 Hz)		
5	1084 (–S–)	8.10—7.20 (8H, m)	7.96 (2H, d, J=8 Hz)	7.57 (2H, d, J=8 Hz)		
18	1087 (–S–)	8.10—7.30 (8H, m)	7.96 (2H, d, J=8 Hz)	7.51 (2H, d, J=8 Hz)		
8	2236 (CN)	8.15—7.20 (9H, m)	7.94 (1H, d, J=9 Hz)	7.12 (1H, d, J=9 Hz)	6.40 (1H, s)	
9	2236 (CN)	8.07—7.15 (8H, m)	7.92 (1H, d, J=8 Hz)	7.09 (1H, d, J=8 Hz)	6.38 (1H, s)	
10	2224 (CN)	7.90—7.25 (4H, m) 7.66 (4H, s)	7.97 (1H, d, J=8 Hz)	7.14 (1H, d, J=8 Hz)	6.54 (1H, s)	
11	2234 (CN)	8.20—7.40 (6H, m) 6.85 (2H, d, J=11 Hz) ($C^{3',5'}$H)	7.99 (1H, d, J=8 Hz)	7.19 (1H, d, J=8 Hz)	6.30 (1H, s)	3.76 (3H, s)

methoxy group. The cyanide ion formed may attack at the cyano carbon of **2** to give sodium 2-quinolinethiolate, followed by reaction with **2** to afford **5**. Actually, the reaction of **2** with sodium cyanide gave **5** and **6**. These sulfides are believed to be formed mainly from **2**, because the reaction of **5** with phenylacetonitrile carbanion afforded only a 19% yield of **8** with recovery of **5** (54%) under the same conditions. The reaction of **2** with diethyl malonate carbanion can be expected to occur at the 2-position carbon (site a), based on the results of the reactions of ethyl cyanoacetate and malononitrile carbanions with **2**, but diethyl 2-quinolinemalonate (**12**) was not obtained from the reaction of **2** with sodium hydride, and instead compounds **5** and **6** were produced. This result may



R	R'	comp.	yield(%)	recovery(%)
$COOC_2H_5$	CN	4	99	—
CN	CN	7	62	—
$COOC_2H_5$	$COOC_2H_5$	12	—	90
Ph	CN	13	89	—
p-ClC_6H_4	CN	14	99	—
p-NCC_6H_4	CN	15	78	—
p-$CH_3OC_6H_4$	CN	16	91	—

Chart 3

be attributed to steric hindrance to the attack of diethyl malonate carbanion on site a, on account of the bulky thiocyanato group of **2**. This conclusion is supported by the following results: whereas the reaction of **3** with carbanions of ethyl cyanoacetate, malononitrile, and various phenylacetonitriles gave the corresponding substitution products, **4** (99%), **7** (62%), α-phenyl- (**13**, 89%), α-(4-chlorophenyl)- (**14**, 99%), α-(4-cyanophenyl)- (**15**, 78%), and α(4-methoxyphenyl)-2-quinolineacetonitrile (**16**, 91%) in high yields, no substitution reaction was observed and 90% of **3** was recovered in the reaction with diethyl malonate carbanion.

It is well known that a chlorine atom located at the α- or γ-position to the ring-nitrogen of aromatic heterocyclic series can be replaced by C-nucleophiles and the reactivity of C-nucleophiles decreases in the following order: benzyl cyanide > ethyl cyanoacetate > diethyl malonate > malononitrile.[2] The more reactive phenylacetonitrile carbanions may attack preferentially at the less reactive sulfur atom (site b), which is less subject to steric effect compared with the 2-position carbon, and the less reactive ethyl cyanoacetate and malononitrile carbanions may attack at the more reactive 2-position carbon (site a). Diethyl malonate carbanion may not react with **2** and **3**, which have a bulky bromine atom or thiocyanato group, owing to the steric effect.

The results may be summarized as follows. The actual reaction site of sites a and b in **2** varies depending upon the nature of the reacting nucleophile. Phenylacetonitrile carbanions attack at the sulfur atom (site b) to give sulfides. Ethyl cyanoacetate and malononitrile carbanions attack at the 2-position carbon (site a) of **2** to give ipso-substition products. Diethyl malonate carbanion does not react at site a, owing to steric hindrance.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 diffraction grating IR spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 60 MHz on a Hitachi R-24B high-resolution NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra (MS) were recorded on a JEOL JMS D-100 mass spectrometer. Samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2, Wakogel C-200 (100—200 mesh).

Preparation of 2-Quinolyl Thiocyanate (2) a) A solution of 2-iodoquinoline[3] (**3**) (500 mg, 1.96 mmol) and KSCN (320 mg, 3.29 mmol) in AcOH (5 ml) was stirred for 2.5 h at 30 °C and then diluted with cold water (50 ml). The precipitate was collected and purified by column chromatography with petroleum benzin–C_6H_6 to give 330 mg (90%) of **2**. MS *m/z*: 256 ($(C_9H_6N)_2$), 186 (M^+), 154 (M^+-S), 128 (M^+-SCN) (see Tables I and II). b) A solution of 2-chloroquinoline (500 mg, 3.06 mmol) and KSCN (500 mg, 5.15 mmol) in AcOH (4 ml) was stirred for 5 h at room temperature and then diluted with cold water (50 ml). The precipitate was collected. The aqueous layer was neutralized with solid Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract and the precipitate were chromatographed using petroleum benzin, petroleum benzin–C_6H_6, and then C_6H_6 as eluents. From the petroleum benzin eluate, 2-chloroquinoline was recovered in 15% yield (75 mg). The petroleum benzin–C_6H_6 eluate gave 290 mg (51%) of **2** and the C_6H_6 eluate afforded 105 mg (12%) of di-2,2′-quinolyl disulfide (**5**), mp 140—142 °C (petroleum benzin) (colorless scales) (lit.,[4] mp 137 °C), which was distinct from compound **17** (di-2-quinolyl sulfide) prepared from **3** and 2-quinolinethiol (**6**).

Di-2-quinolyl Sulfide (17) Compound **3** (300 mg, 1.17 mmol) was added to a solution of **6** (210 mg, 1.3 mmol) and NaOH (60 mg, 1.5 mmol) in HMPA (3 ml). The mixture was stirred for 2 h at 50 °C, diluted with water, neutralized with AcOH, and extracted with C_6H_6. The C_6H_6 extract was purified by chromatography to give 155 mg (83%) of **17**, colorless needles (petroleum benzin), mp 186—188 °C (lit.,[5] mp 188 °C).

Reaction of 2 with Diethyl Malonate As a typical procedure, a solution of diethyl malonate (2.6 mmol) and 60% NaH (in oil, 290 mg, 7.25 mmol) in HMPA (4 ml) was stirred for 30 min in a cold water bath. Then **2** (300 mg, 1.6 mmol) was added, and the mixture was stirred under a nitrogen atmosphere for 2 h at room temperature, poured into ice-water, neutralized with AcOH, and extracted with C_6H_6. The C_6H_6 extract was chromatographed using C_6H_6 and then C_6H_6–$CHCl_3$ as eluents. The C_6H_6 eluate afforded 55 mg (21%) of **5**. The crude product obtained from the C_6H_6–$CHCl_3$ eluate was recrystallized from MeOH to give 150 mg (58%) of **6**, yellow needles, mp 174—175 °C (lit.,[6] mp 175 °C).

Reaction of 2 with Ethyl Cyanoacetate According to the procedure described above, the C_6H_6 extract was chromatographed using C_6H_6 and then C_6H_6–$CHCl_3$ as eluents. The first C_6H_6 eluate gave 50 mg (19%) of **5**. The crude product obtained from the second C_6H_6 eluate was recrystallized from petroleum benzin–C_6H_6 to give 200 mg (52%) of ethyl α-cyano-2-quinolineacetate (**4**), yellow plates, mp 165—166 °C (lit.,[3] mp 166 °C). IR (KBr): 2188 (CN), 1650 (CO) cm^{-1}. The C_6H_6–$CHCl_3$ eluate afforded 35 mg (14%) of **6**.

Reaction of 2 with Malononitrile According to the procedure described above, the residue not extracted with C_6H_6 was collected and recrystallized from MeOH to give 220 mg (71%) of 2-quinolinemalononitrile (**7**), yellow needles, mp 300—301 °C (lit.,[7] mp 301 °C). IR (KBr): 2178, 2204 (CN) cm^{-1}. The C_6H_6 extract was chromatographed using C_6H_6 and then C_6H_6–$CHCl_3$ as eluents. The C_6H_6 eluate gave 25 mg (10%) of **5** and the C_6H_6–$CHCl_3$ eluate afforded 20 mg (8%) of **6**.

Reaction of 2 with Phenylacetonitriles According to the procedure described above, the C_6H_6 extract was chromatographed using petroleum benzin–C_6H_6, C_6H_6, and then C_6H_6–$CHCl_3$ as eluents. The crude product obtained from the petroleum benzin–C_6H_6 eluate was recrystallized from petroleum benzin to give the sulfide. The C_6H_6 eluate afforded **5** and the C_6H_6–$CHCl_3$ eluate gave **6**. The reactions of **2** (300 mg, 1.6 mmol) with phenyl-, *p*-chlorophenyl-, and *p*-cyanophenylacetonitrile gave the corresponding α-(2-quinolylthio)- (**8**, 350 mg, 79%), α-(2-quinolylthio)-4-chloro- (**9**, 475 mg, 95%), and α-(2-quinolylthio)-4-cyanophenylacetonitrile (**10**, 390 mg, 80%). The reaction with *p*-methoxyphenylacetonitrile afforded α-(2-quinolylthio)-4-methoxyphenylacetonitrile (**11**, 155 mg, 31%), **5** (30 mg, 12%), and **6** (95 mg, 37%) (in the presence of 2.75 mmol (110 mg) of 60% NaH, **11** (140 mg, 28%), **5** (85 mg, 33%) and **6** (75 mg, 29%) were obtained) (see Tables I and II).

Reaction of 2 with NaH According to the procedure described above, the reaction was carried out in the absence of C-nucleophile to give 135 mg (52%) of **5** and 90 mg (35%) of **6**.

Reaction of 2 with 6 A solution of **6** (130 mg, 0.8 mmol) and 60% NaH (in oil, 40 mg, 1.0 mmol) in HMPA (4 ml) was stirred for 30 min in a cold water bath, then **2** (150 mg, 0.8 mmol) was added to the solution. The reaction was carried out according to the procedure described above to give **5** (225 mg, 87%) together with recovery of **6** (30 mg, 12%).

Reaction of 2 with NaCN According to the procedure described above, a solution of **2** (300 mg, 1.6 mmol) and NaCN (100 mg, 2.0 mmol) in HMPA (4 ml) provided 60 mg (23%) of **5** and 175 mg (67%) of **6**.

Reaction of 5 with Phenylacetonitrile A solution of phenylacetonitrile (125 mg, 1.0 mmol) and 60% NaH (in oil, 100 mg, 2.5 mmol) in HMPA (2 ml) was stirred for 30 min in a cold water bath, then **5** (250 mg, 0.8 mmol) was added to the solution. According to the procedure described above, the C_6H_6 extract was chromatographed using petroleum benzin–

C_6H_6, C_6H_6, and then C_6H_6–$CHCl_3$ as eluents to give 40 mg (19%) of **8**, 135 mg (54%) of **5**, and 35 mg (14%) of **6**.

Reaction of 3 with C-Nucleophiles A solution of C-nucleophile (1.3 mmol) and 60% NaH (in oil, 145 mg, 3.6 mmol) in HMPA (2 ml) was stirred for 30 min in a cold water bath, then **3** (200 mg, 0.8 mmol) was added to the solution. The mixture was stirred for 2 h at room temperature, poured into ice-water, neutralized with AcOH, and extracted with C_6H_6. The C_6H_6 extract was purified by chromatography. The reaction of **3** with ethyl cyanoacetate gave 190 mg (99%) of **4**. Malononitrile gave 115 mg (62%) of **7**. α-Phenyl-2-quinolineacetonitrile (**13**) from phenylacetonitrile had mp 92—93 °C (pale yellow needles, petroleum benzin) (lit.,[2] mp 93 °C). Yield, 175 mg (89%). IR (KBr): 2236 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$): 5.43 (1H, s, CH), 7.00—7.85 (10H, m, aromatic H), 8.03 (1H, d, $J=8$ Hz, C^4-H). α-(4-Chlorophenyl)-2-quinolineacetonitrile (**14**) from *p*-chlorophenylacetonitrile had mp 150—152 °C (orange needles, petroleum benzin–C_6H_6). Yield, 220 mg (99%). *Anal.* Calcd for $C_{17}H_{11}ClN_2$: C, 73.25; H, 3.98; N, 10.05. Found: C, 73.40; H, 3.91; N, 9.81. IR (KBr): 2170 (CN) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 6.05 (1H, s, CH), 6.60—8.50 (10H, m, aromatic H). α-(4-Cyanophenyl)-2-quinolineacetonitrile (**15**) from *p*-cyanophenylacetonitrile had mp 194—196 °C (orange needles, C_6H_6–$CHCl_3$). Yield, 165 mg (78%). *Anal.* Calcd for $C_{18}H_{11}N_3O$: C, 80.28; H, 4.12; N, 15.60. Found: C, 80.00; H, 4.13; N, 15.28. IR (KBr): 2156, 2222 (CN) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 6.30 (1H, s, CH), 7.00—8.50 (10H, m, aromatic H). α-(4-Methoxyphenyl)-2-quinolineacetonitrile (**16**) from *p*-methoxyphenylacetonitrile had mp 146—147 °C (pale yellow needles, petroleum benzin). Yield, 200 mg (91%). *Anal.* Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.87; H, 5.09; N, 9.91. IR (KBr): 2236 (CN) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.76 (3H, s, OCH_3), 6.04 (1H, s, CH), 6.80—8.55 (10H, m, aromatic H). In the reaction with diethyl malonate, only 180 mg (90%) of **3** was recovered.

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