Heteroatom Chemistry
Volume 11, Number 6, 2000

Synthesis of Quinazolines Using Carbon Dioxide (or Carbon Monoxide with Sulfur) under Mild Conditions

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Received 30 May 2000; revised 13 July 2000

ABSTRACT: *Sulfur-assisted carbonylation of 2-aminobenzonitriles with carbon monoxide using K_2CO_3 as a base under ambient conditions (1 atm, 20°C) to afford 2-hydroxy-4-mercaptoquinazolines in excellent yields was found. This carbonylation was applied to chemical fixation of carbon dioxide under mild conditions. Carbon dioxide (1 atm) easily reacted with 2-aminobenzonitriles at 20°C assisted by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give 2,4-dihydroxyquinazolines in excellent yields.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:428–433, 2000

INTRODUCTION

Substituted 2,4-dihydroxyquinazolines **1** are of interest because of their biological activities. For example, 7-chloro-1-carboxymethyl-3-(4′-bromo-2′-fluorophenylmethyl)-2,4(1H,3H)quinazolinone (FK 366, Zenarestat) was developed as an aldose reductase inhibitor for a remedy of complications of diabetes mellitus (Figure 1) [1].

Generally, synthesis of **1** is carried out by use of anthranilic acid with urea[2], anthranilamide with phosgene [3], and anthranilic acid with potassium cyanate[4] or chlorosulfonyl isocyanate [5]. However, these methods are considerably limited because of high toxicity of the reagents or the use of drastic conditions.

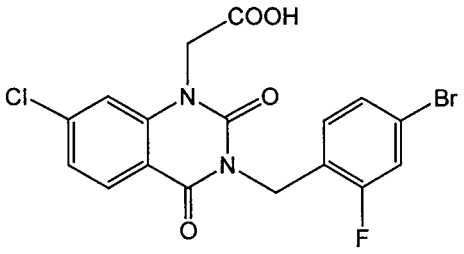

FIGURE 1 FK 366, Zenarestat.

Recently, we developed the sulfur-assisted carbonylation of 2-aminobenzamides with carbon monoxide in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) to afford 2,4-dihydroxyquinazolines **1** under severe reaction conditions. Furthermore, the reaction of 2-aminobenzonitrile (**2a**) using carbon monoxide, sulfur, and water caused an addition reaction of hydrogen sulfide, generated in situ, to the cyano group under pressurized and moderate temperature conditions (30 atm, 80°C), to form 2-hydroxy-4-mercaptoquinazoline (**3a**) directly [6].

We herein wish to report new and convenient syntheses of 2-hydroxy-4-mercaptoquinazolines **3** from 2-aminobenzonitriles **2**, carbon monoxide, and sulfur (or carbonyl sulfide), and 2,4-dihydroxyquinazolines **1** from 2-aminobenzonitriles **2** and carbon

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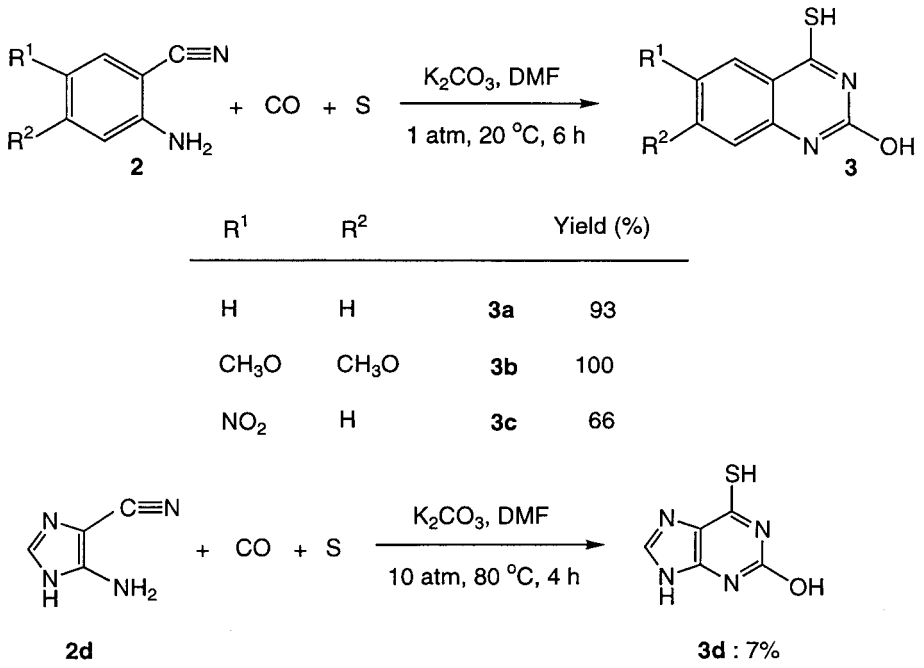


SCHEME 1

dioxide under mild conditions (1 atm, 20°C) in the presence of an appropriate base (K_2CO_3 or DBU) [7].

RESULTS AND DISCUSSION

At the outset, synthesis of 2-hydroxy-4-mercaptoquinazoline (**3a**) from 2-aminobenzonitrile (**2a**) with powdered sulfur in the presence of potassium carbonate in DMF was performed at room temperature (r.t.) (20°C) under a CO atmosphere (1 atm) for 6 hours. The pure carbonylation and cyclization easily proceeded under mild conditions to give 2-hydroxy-4-mercaptoquinazoline (**3a**) in a 93% yield (Scheme 1).

Next, a variety of bases was examined for the synthesis of **3a** as a model using carbon monoxide with sulfur under similar reaction conditions for 6 hours (Table 1). K_2CO_3, DBU, and triethylamine brought about the synthesis of **3a** in excellent yields (93%, 90%, 85% respectively). However, NaOH gave a poor yield of **3a** (42%), and other bases ($NaHCO_3$, pyridine, and none) did not give **3a** at all.

Several substituted 2-hydroxy-4-mercaptoquinazolines **3** were prepared using the carbon monoxide and sulfur system in the presence of K_2CO_3 under similar mild conditions in good to excellent yields (66–100%) (Scheme 1). However, carbonylation of 5-amino-4-cyanoimidazole (**2d**) was sluggish, and 2-hydroxy-6-mercaptopurine (**3d**) was not obtained under similar mild conditions. Even under severe reaction conditions (10 atm, 80°C, 4 hours), the yield of **3d** remained low (7%).

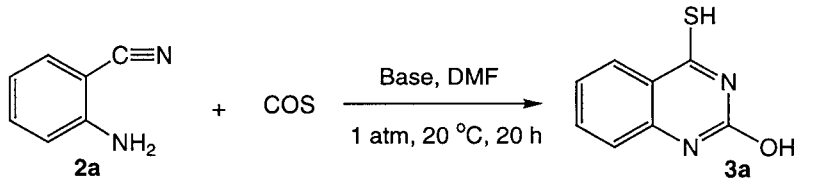
TABLE 1 Effect of Bases for Synthesis of **3a**

Base	*Yield* (%)
K_2CO_3	93
DBU[a]	90
Et_3N	85
NaOH	42
$NaHCO_3$	0
Pyridine	0
none	0

[a]1,8-Diazabicyclo[5.4.0]undec-7-ene.

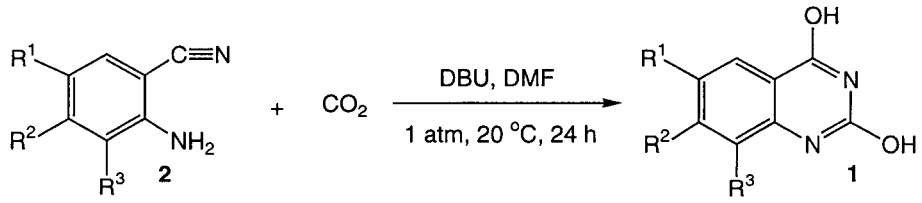
Furthermore, we found that the cyclization of 2-aminobenzonitrile (**2a**) with carbonyl sulfide gave 2-hydroxy-4-mercaptoquinazoline (**3a**) under similar mild conditions (1 atm 20°C) (Scheme 2) [8]. By use of DBU as a base, **3a** was obtained in quantitative yield (100%). The use of K_2CO_3 also gave **3a** in moderate yield (45%).

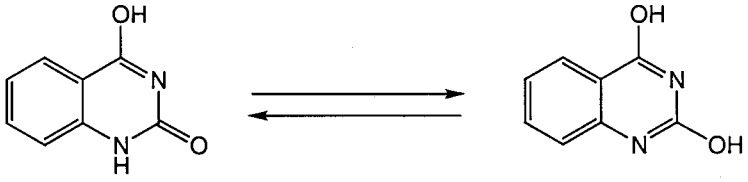
Next, the carbonylation of 2-aminobenzonitriles **2** with carbon dioxide to form 2,4-dihydroxyquinazolines **1** under mild conditions (Scheme 3) was effected. 2,4-Dihydroxyquinazoline (**1a**) was synthesized from 2-aminobenzonitrile (**2a**) using DBU in DMF under 1 atm of CO_2 at r.t. (20°C) for 24 hours. This chemical fixation of carbon dioxide proceeded smoothly to afford 2,4-dihydroxyquinazoline (**1a**) in an excellent yield (97%).



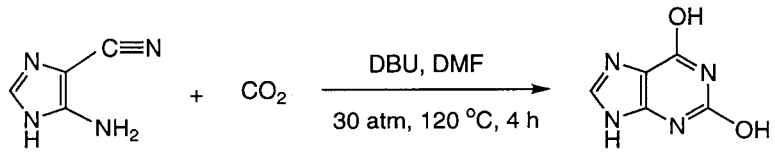
3a : 100% (DBU), 45% (K_2CO_3)

SCHEME 2





R^1	R^2	R^3		Yield (%)
H	H	H	**1a**	97
CH_3O	CH_3O	H	**1b**	97
NO_2	H	H	**1c**	90
NO_2	H	Br	**1d**	100



1e : 52%

SCHEME 3

Various bases were examined for this carbonylation of **2a** using carbon dioxide under similar reaction conditions for 24 hours (Table 2). DBU and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) gave the best results of synthesis of **1a** (97%, 94%, respectively). However, a shorter reaction time (6 hours) lowered the yield of **1a** (57%). Also by use of severe reaction conditions (10 atm, 80°C), **1a** was obtained quantitatively (98%) after a short reaction time (1 hour). However, other bases (Dabco (1,4-diazabicyclo[2.2.2]-octane), triethylamine, pyridine, K_2CO_3, $NaHCO_3$, NaOH, and none) did not give the product (**1a**) at all. These results agreed with the reported carbonylation reaction with carbon dioxide using DBU, where a CO_2-DBU complex formed from carbon dioxide, and DBU is considered to be an active species for carboxylation [10].

Several 2,4-dihydroxyquinazolines (**1a–d**) were synthesized similarly from the corresponding 2-aminobenzonitriles (**2a–d**), substituted by either an elec-

TABLE 2 Effect of Bases for Synthesis of **1a**

Base	*Yield* (%)
DBU[a]	97 (57[b], 98[c])
DBN[d]	94
Dabco[e]	0
K_2CO_3	0
Et_3N	0
NaOH	0
$NaHCO_3$	0
Pyridine	0
none	0

[a]1,8-Diazabicyclo[5.4.0]undec-7-ene.
[b]6 h.
[c]10 atm, 80°C, 1 hour.
[d]1,5-Diazabicyclo[4.3.0]undec-5-ene.
[e]1,4-Diazabicyclo[2.2.2]octane.

tron donating-group or an electron-withdrawing group, with carbon dioxide in the presence of DBU in excellent yields (Scheme 3). Xanthine (**1e**) was obtained from 5-amino-4-cyanoimidazole (**2e**) in 52% yield under severe reaction conditions (30 atm, 120°C, 4 hours).

Scheme 4 shows a plausible pathway for the formation of **1a** from **2a** with carbon dioxide aided by DBU [11]. The carbonylation of **2a** with carbon dioxide generates a carbamate salt (**4a**) in the presence of DBU. Then, nucleophilic cyclization of **4a** into **5a,** followed by rearrangement of **5a,** gives **6a.** Finally, acidification of **6a** affords the final product (**1a**). In this reaction system, the formation of isocyanate as an intermediate from the carbamate salt (**4a**) might be impossible under mild conditions. An industrial urea synthesis in which an isocyanate is a key intermediate is performed under high pressure and temperature [12].

From the viewpoint of simple operation, mild conditions, good yields and high purities of products, safety of reagents, and utilization of carbon monoxide and carbon dioxide, the present reaction may provide us with a useful method for the synthesis of substituted 2-hydroxy-4-mercaptoquinazolines **3** and 2,4-dihydroxyquinazolines **1.**

EXPERIMENTAL

General

Melting points were determined on a Mettler FP 5 instrument and were uncorrected. FT-IR spectra were recorded on a Nicolet Magna-IR 550 instrument. ^1H and ^{13}C NMR spectra were obtained on a JEOL JNM-AL300 (300 MHz, 75 Mhz) instrument. Chemical shifts were reported in ppm relative to tetramethylsilane (δ-units). Mass and exact mass spectra were recorded on a JEOL JMS-AX505HA spectrometer.

2-Aminobenzonitriles **2,** DMF, bases, powdered sulfur (99.5%), carbon monoxide (99.9%), and carbon dioxide (99.8%) were used as purchased.

Carbonyl sulfide was prepared from carbon monoxide with sulfur in the presence of a selenium catalyst [13].

General Procedure for Synthesis of 2-Hydroxy-4-mercaptoquinazoline (**3a**) *from Carbon Monoxide with Sulfur*

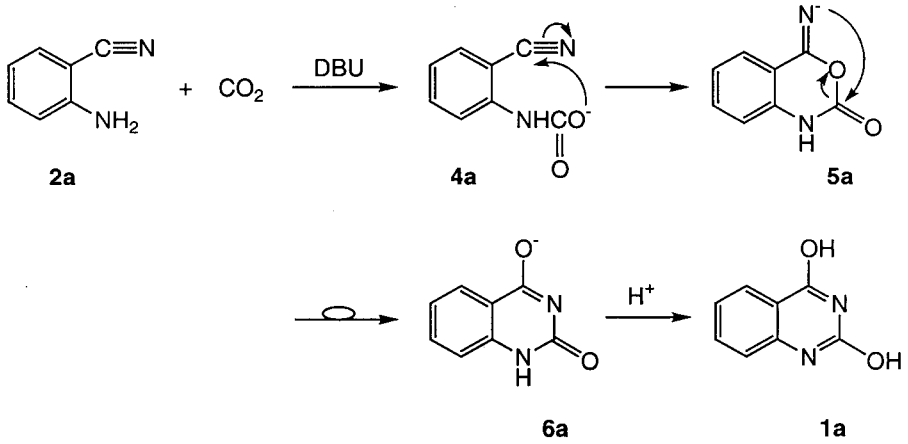
Into a DMF solution (20 mL) of powdered sulfur (0.962 g, 30 mmol) and K_2CO_3 (4.15 g, 30 mmol), 2-aminobenzonitrile (**2a**) (1.18 g, 10 mmol) was added. The solution was vigorously stirred under carbon monoxide (1 atm) at 20°C for 6 hours. The reaction mixture was then poured into 1N HCl (200 mL). A solid that deposited was collected on a glass filter and was washed with toluene (200 mL) and diethyl ether (200 mL). 2-Hydroxy-4-mercaptoquinazoline (**3a**) (1.66 g, 93%) was obtained in pure form.

*2-Hydroxy-4-mercaptoquinazoline (***3a***).* m.p. 285.2°C (Ref. [6] 271.4°C); IR (KBr) 3430, 1725 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 7.16–7.20 (m, 2H), 7.65 (t, J = 8 Hz, 1H), 8.29 (d, J = 8 Hz, 1H), 11.63 (s, 1H), 12.74 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 115.8, 120.1, 123.1, 130.4, 135.5, 138.1, 147.3, 192.0; MS (*m/z, %*) 178 (M^+, 100), 150 (55), 145 (32), 135 (45), 108 (32); Exact MS calcd. for $C_8H_6N_2OS$: 178.0201. Found: 178.0187.

6,7-Dimethoxy-2-hydroxy-4-mercaptoquinazoline (**3b**). m.p. 276.2°C; IR (KBr) 3450, 1710 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 3.77 (s, 3H), 3.83 (s, 3H), 6.64 (s, 1H), 7.66 (s, 1H), 11.45 (s, 1H), 12.45 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 55.6, 56.0, 97.3, 110.0, 113.4, 134.3, 145.7, 147.4, 156.0, 189.3; MS (*m/z, %*) 238 (M^+, 100), 223 (32); Exact MS calcd. for $C_{10}H_{10}N_2O_3S$: 238.0412. Found: 238.0390.

2-Hydroxy-4-mercapto-6-nitroquinazoline (**3c**). m.p. > 300°C; IR (KBr) 3340, 3215, 1710 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 7.31 (d, J = 9 Hz, 1H), 8.41 (d, J = 9 Hz, 1H), 9.00 (s, 1H), 12.16 (s, 1H), 13.11 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 117.4, 119.8, 126.2, 129.5, 142.5, 143.0, 146.9, 190.9; MS (*m/z, %*) 223 (M^+, 100), 177 (13), 105 (11); Exact MS calcd. for $C_8H_5N_3O_3S$: 223.0052. Found: 223.0030.

2-Hydroxy-6-mercaptopurine (**3d**). m.p. > 300°C; IR (KBr) 3445, 1695, 1610 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 5.50 (brs, 1H), 8.03 (s, 1H),



SCHEME 4

12.05 (s, 1H), 12.17 (brs, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 118.2, 143.6, 145.0, 149.2, 176.3; MS (*m/z, %*) 168 (M^+, 100), 125 (25); Exact MS calcd. for $C_5H_4N_4OS$: 168.0106. Found: 168.0104.

Preparation of 2-Hydroxy-4-mercaptoquinazoline (**3a**) *from 2-Aminobenzonitrile* (**2a**) *and Carbonyl Sulfide*

A DMF solution (20 mL) of 2-aminobenzonitrile (**2a**) (1.18 g, 10 mmol) and DBU (4.49 mL, 30 mmol) was vigorously stirred under an argon atmosphere (1 atm) at 20°C. Carbonyl sulfide (1 atm) with argon was introduced slowly during 1 hour at 20°C, and the solution was stirred for an additional 19 hours at 20°C. The reaction mixture was poured into 1N HCl (100 mL), and the solid that deposited was washed with toluene (50 mL) and *t*-butyl methyl ether (150 mL). 2-Hydroxy-4-mercaptoquinazoline (**3a**) (1.78 g, 100%) was obtained.

Typical Procedure for Synthesis of 2,4-Dihydroxyquinazoline (**1a**) *Using Carbon Dioxide*

A DMF solution (20 mL) containing 2-aminobenzonitrile (**2a**) (1.18 g, 10 mmol) and DBU (4.49 mL, 30 mmol) was vigorously stirred under carbon dioxide (1 atm) at 20°C for 24 hours. The reaction mixture was then poured into 1N HCl (200 mL), and the solid that deposited was washed with toluene (100 mL) and diethyl ether (100 mL). 2,4-Dihydroxyquinazoline (**1a**) was obtained in a 97% yield (1.57 g).

2,4-Dihydroxyquinazoline (**1a**). m.p. > 300°C (Ref. [14] > 350°C); IR (KBr) 3255, 3055, 1705 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.13–7.18 (m, 2H), 7.61 (t, J = 8 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 11.11 (s, 1H), 11.25 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 114.3, 115.3, 122.3, 126.9, 134.9, 140.8, 150.3, 162.8; MS (*m/z, %*) 162 (M^+, 100), 119 (48), 92 (17); Exact MS calcd for $C_8H_6N_2O_2$: 162.0429. Found: 162.0408.

2,4-Dihydroxy-6,7-dimethoxyquinazoline (**1b**). m.p. > 300°C; IR (KBr) 3470, 1710 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.77 (s, 3H), 3.81 (s, 3H), 6.67 (s, 1H), 7.24 (s, 1H), 10.91 (s, 1H), 11.08 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 55.7, 55.8, 97.8, 106.2, 107.2, 136.5, 145.0, 150.4, 154.9, 162.4; MS (*m/z, %*) 222 (M^+, 100), 207 (38), 164 (22); Exact MS calcd for $C_{10}H_{10}N_2O_4$: 222.0641. Found: 222.0642.

2,4-Dihydroxy-6-nitroquinazoline (**1c**). m.p. > 300°C; IR (KBr) 3455, 1680 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.26 (dd, J = 2, 9 Hz, 1H), 8.38 (td, J = 2, 9 Hz, 1H), 8.50 (d, J = 2 Hz, 1H), 11.65 (s, 1H), 11.71 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 114.4, 116.6, 123.0, 129.5, 141.8, 145.6, 149.9, 161.5; MS (*m/z, %*) 207 (M^+, 100), 164 (27); Exact MS calcd for $C_8H_5N_3O_4$: 207.0280. Found: 207.0271.

8-Bromo-2,4-dihydroxy-6-nitroquinazoline (**1d**). m.p. > 300°C; IR (KBr) 3175, 3080, 1700 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.51 (d, J = 2 Hz, 1H), 8.60 (d, J = 2 Hz, 1H), 10.95 (s, 1H), 11.89 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 108.6, 116.1, 122.1, 132.4, 141.7, 143.9, 149.5, 160.8; MS (*m/z, %*) 287 (98), 285 (M^+, 100), 244 (39), 242 (40), 152 (35), 151 (35); Exact MS calcd for $C_8H_4BrN_3O_4$: 284.9385. Found: 284.9370.

Xanthine (**1e**). m.p. > 300°C (Ref. [15] Decomposition on heating without melting and with partial sublimation); IR (KBr) 3005, 1705 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.80 (brs, 1H), 7.98 (s, 1H), 10.85 (s, 1H), 11.57 (brs, 1H); ^{13}C NMR (75 MHz, d_6-

DMSO) δ 106.7, 140.3, 148.3, 151.3, 155.4; MS (*m/z*, %) 152 (M^+, 100), 109 (52), 54 (38); Exact MS calcd for $C_5H_4N_4O_2$: 152.0334. Found: 152.0332.

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