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Highly efficient synthesis of 1*H*-quinazoline-2,4-diones using carbon dioxide in the presence of catalytic amount of DBU

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Abstract—The first example of chemical fixation of carbon dioxide in the presence of catalytic amount of DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene) or DBN (1,5-diazabicyclo[4.3.0]non-5-ene) was developed. Carbon dioxide easily reacted with 2-aminobenzonitriles under mild conditions (1 atm, 20 °C), assisted by excess amount of DBU or DBN to give corresponding 1*H*-quinazoline-2,4-diones in excellent yields. Also, catalytic amount of DBU or DBN is effective for the synthesis of 1*H*-quinazoline-2,4-diones. Using catalytic amount of DBU (0.05 equiv.), 7-chloro-1*H*-quinazoline-2,4-diones which is a key intermediate of medicines (FK366, Zenarestat® and KF31327) was synthesized successfully in a 90% yield under the CO_2 pressure of 10 atm at 80°C.

1. Introduction

Use of chemical fixation of carbon dioxide on the fine chemicals production is of importance for both the environmental problems of global warming and the effective utilization of chemical resources. Carbon dioxide is also an attractive C_1 building block in organic synthesis as it is highly abundant, inexpensive, nontoxic, and nonflammable. However, due to the inert nature of carbon dioxide, efficient catalytic processes for chemical fixation remain significant synthetic challenges.

We developed a new chemical fixation of carbon dioxide to form substituted 1*H*-quinazoline-2,4-diones **1** which is useful for the synthesis of medicine intermediates. Substituted 1*H*-quinazoline-2,4-diones **1** have been interesting for their biological activities. For example, 7-chloro-1*H*-quinazoline-2,4-diones (**1g**) is a key intermediate for the production of the following medicines. FK 366 (Zenarestat®) showed the effect for an aldose reductase inhibitor, and was produced for a remedy of complications of diabetes mellitus,[1a,b] and KF31327 was developed as a heart disease remedy and an impotence medicine[2] (Fig. 1). The conventional syntheses of **1** are carried out by anthranilic acid with urea,[3a,b] anthranilamide with phosgene,[4] and anthranilic acid with potassium cyanate[5] or chlorosulfonyl isocyanate.[6] However, these synthetic methods are considerably limited because of high toxicity of the reagents or the use of drastic conditions.

We report here the full results of our investigations on a convenient synthesis of 1*H*-quinazoline-2,4-diones **1** from 2-aminobenzonitriles **2** by the chemical fixation of carbon dioxide under mild conditions (1 atm, 20°C) in the presence of excess amount of DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) or DBN (1,5-diazabicyclo[4.3.0]non-5-ene).[7,8] Furthermore, we established the first example of chemical fixation of carbon dioxide in the presence of catalytic amount of DBU or DBN.

2. Results and discussion

Our initial studies showed that successful synthesis of 1*H*-quinazoline-2,4-dione (**1a**) from 2-aminobenzonitrile (**2a**) with 3.0 equiv. of DBU in DMF was performed at

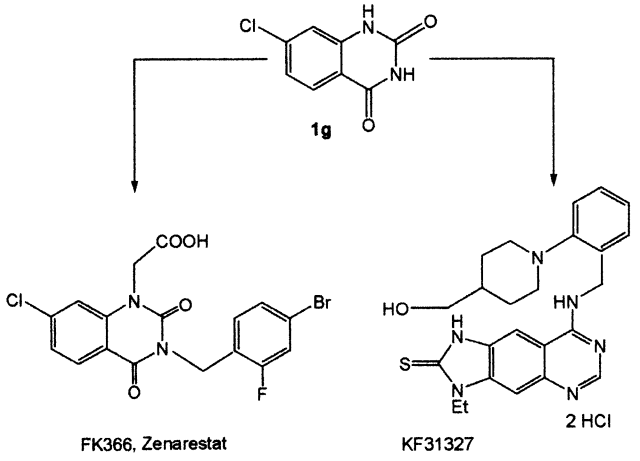

Figure 1. 7-Chloro-1*H*-quinazoline-2,4-dione (**1g**) is a key intermediate of FK 366 (Zenarestat®) and KF31327.

Keywords: carbon dioxide; carbonylation; cyclyzation; catalytic; quinazolines; quinazolidinones.

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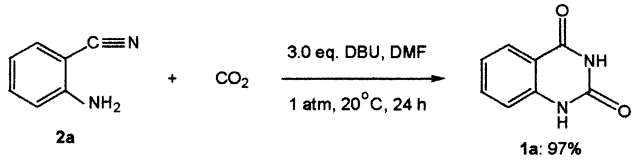
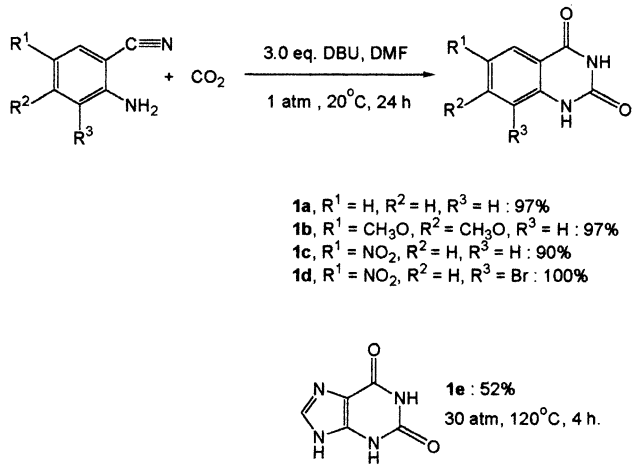


Scheme 1.

Table 1. Effect of bases (3.0 equiv.) for synthesis of **1a**

Entry	Base	Yield %
1	DBU[a]	97
2	DBU	57[b]
3	DBU	98[c]
4	DBN[d]	94
5	Dabco[e]	0
6	K_2CO_3	0
7	Et_3N	0
8	NaOH	0
9	$NaHCO_3$	0
10	Pyridine	0
11	None	0

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



Scheme 2.

room temperature (20°C) under a CO_2 atmosphere (1 atm) for 24 h. The pure carbonylation and cyclization easily proceeded under mild conditions to give 1*H*-quinazoline-2,4-dione (**1a**) in a 97% yield (Scheme 1).

A variety of bases was investigated as catalysts for this CO_2 fixation under similar mild conditions for 24 h (Table 1). DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or DBN (1,5-diazabicyclo[4.3.0]non-5-ene) gave the best results of synthesis of **1a** (97, 94%, respectively) (entries 1 and 4). However, a shorter reaction time (6 h) lowered the yield of **1a** (57%) (entry 2). Also by use of severe reaction conditions (10 atm, 80°C), **1a** was obtained quantitatively (98%) after a short reaction time (1 h) (entry 3). However, other bases (Dabco® (1,4-diazabicyclo[2.2.2]-octane), K_2CO_3, triethylamine, NaOH, $NaHCO_3$, pyridine, and none) did not give the product (**1a**) at all (entries 5–11). 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 was considered to be an active species for carboxylation.[9a–c]

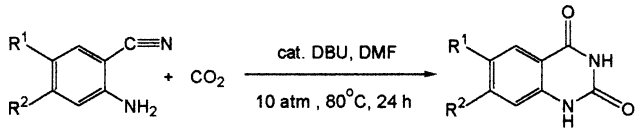
Several 1*H*-quinazoline-2,4-diones (**1a–d**) were synthesized similarly from the corresponding 2-aminobenzonitriles (**2a–d**), substituted by either an electron donating group or electron withdrawing groups, with carbon dioxide in the presence of 3.0 equiv. of DBU under mild conditions (1 atm, 20°C) in excellent yields (Scheme 2). Xanthine (**1e**) was obtained from 5-amino-4-cyanoimidazole (**2e**) in 52 % yield under 30 atm, 120°C for 4 h.

Excess amount (3.0 equiv.) of DBU or DBN showed the effective chemical fixation of carbon dioxide to synthesize 1*H*-quinazoline-2,4-diones (**1a–d**) from 2-aminobenzonitriles (**2a–d**) under mild conditions (1 atm, 20°C). However, from the viewpoint of application of the present reaction to actual industrial production of **1**, an efficient catalytic process (using catalytic amount of DBU) for chemical fixation of carbon dioxide is very significant.

Therefore, effect of catalytic amount of DBU was examined for the synthesis of 1*H*-quinazoline-2,4-dione (**1a**) from 2-aminobenzonitrile (**2a**) with carbon dioxide as a model (Table 2). Under 1 atm, 20°C, more than 1.0 equiv. of DBU was necessary to obtain quantitative yields of **1a** (entries 1–3). However, using 0.1 equiv. of DBU under

Table 2. Effect of reaction conditions for synthesis of **1a**

Entry	Base	Amount of base equiv.	Solvent	Pressure (atm)	Temperature (°C)	Time (h)	Yield %
1	DBU	3.0	DMF	1	20	24	97
2	DBU	1.0	DMF	1	20	24	96
3	DBU	0.5	DMF	1	20	24	64
4	DBU	0.5	DMF	1	20	48	77
5	DBU	0.1	DMF	1	20	48	21
6	DBU	3.0	DMF	10	80	1	98
7	DBU	0.5	DMF	10	80	24	96
8	DBU	0.1	DMF	10	80	24	94
9	DBU	0.1	DMF	10	80	6	84
10	DBU	0.05	DMF	10	80	24	91
11	DBU	0.01	DMF	10	80	24	46
12	DBU	0.05	THF	10	80	24	71
13	DBU	0.05	DMSO	10	80	24	93
14	DBN	0.05	DMF	10	80	24	76



1a, R^1 = H, R^2 = H : 94% (0.1eq.), 91% (0.05 eq.)
1b, R^1 = CH_3O, R^2 = CH_3O : 99% (0.1 eq.), 92% (0.05 eq.)
1c, R^1 = NO_2, R^2 = H : 82% (0.5 eq.)
1f, R^1 = Cl, R^2 = H : 98% (0.1 eq.), 97% (0.05 eq.)
1g, R^1 = H, R^2 = Cl : 89% (0.1 eq.), 90% (0.05 eq.)

Scheme 3.

mild conditions, turnover number reached to 2.1 (entry 5). Next, catalytic activity of DBU was tested under 10 atm, 80°C. Surprisingly, 0.05 equiv. of DBU gave the excellent yield (91%) of 1*H*-quinazoline-2,4-dione (**1a**) (entry 10). This is the first example of chemical fixation of carbon dioxide in the presence of catalytic amount of DBU. Moreover, in the presence of 0.01 equiv. of DBU under 10 atm, 80°C, turnover number rose to 46 (entry 11). DMSO was similarly effective as a solvent, high yield of **1a** (93%) was obtained using 0.05 equiv. of DBU (entry 13). However, yield of **1a** was lowered using THF (71%), because of low solubility of **1a** in THF (entry 12). DBN (0.05 equiv.) also showed excellent catalytic activity for the carbonylation of 2-aminobenzonitrile (**2a**) with carbon dioxide, 1*H*-quinazoline-2,4-dione (**1a**) afforded in good yield (76%) (entry 14).

In the presence of 0.1 or 0.05 equiv. of DBU under 10 atm, 80°C for 24 h, 1*H*-quinazoline-2,4-diones (**1a**,**b**,**f** and **g**) were synthesized from the corresponding 2-aminobenzonitriles (**2a**,**b**,**f**,**g**) substituted by functional group, with carbon dioxide in excellent yields (Scheme 3). However, preparation of **1c** in reasonable yield needed 0.5 equiv. of DBU, because of low basicity of **2c** substituted by nitro group. 7-Chloro-1*H*-quinazoline-2,4-dione (**1g**) which is a key intermediate of medicines (FK366, Zenarestat® and KF31327) was also synthesized in a 90% under 10 atm, 80°C for 24 h using 0.05 equiv. of DBU.

Fig. 2 shows a plausible pathway for the formation of **1a** from **2a** with carbon dioxide aided by catalytic amount of DBU. The carbonylation of **2a** with carbon dioxide generates a carbamate salt (**4a**) in the presence of catalytic DBU. Then, nucleophilic cyclization of **4a** into **5a**, followed by rearrangement of **5a**, gives **6a**. Finally, formation of aromatic ring of **6a** affords the final product (**1a**). In this DBU catalyzed reaction system which proceeds, even if under 1 atm, 20°C, the formation of isocyanate as an intermediate from the carbamate salt (**4a**) might be impossible. An industrial urea synthesis in which an isocyanate is a key intermediate is performed under high pressure and temperature.[10]

3. Conclusion

Carbon dioxide smoothly reacted with 2-amino-benzonitriles **2** under mild conditions (1 atm, 20°C), assisted by excess amount of DBU or DBN to give corresponding 1*H*-quinazoline-2,4-diones **1** in excellent yields. Also, 1*H*-quinazoline-2,4-diones **1** was synthesized in the presence of catalytic amount of DBU or DBN effectively. Moreover, 7-chloro-1*H*-quinazoline-2,4-dione (**1g**) which is a key intermediate of medicines (FK366, Zenarestat® and KF31327) was prepared in a 90% under 10 atm, 80°C using 0.05 equiv. of DBU.

4. Experimental

4.1. 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. ^{1}H 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-600 spectrometer. 2-Aminobenzonitriles **2**, DMF, THF, DMSO, bases, carbon dioxide (99.8%) were used as purchased.

4.2. Typical procedure for synthesis of 1*H*-quinazoline-2,4-dione (1a) using excess amount of DBU

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 h. The reaction mixture was then poured into 1 N HCl (200 mL), and the solid that deposited was washed with

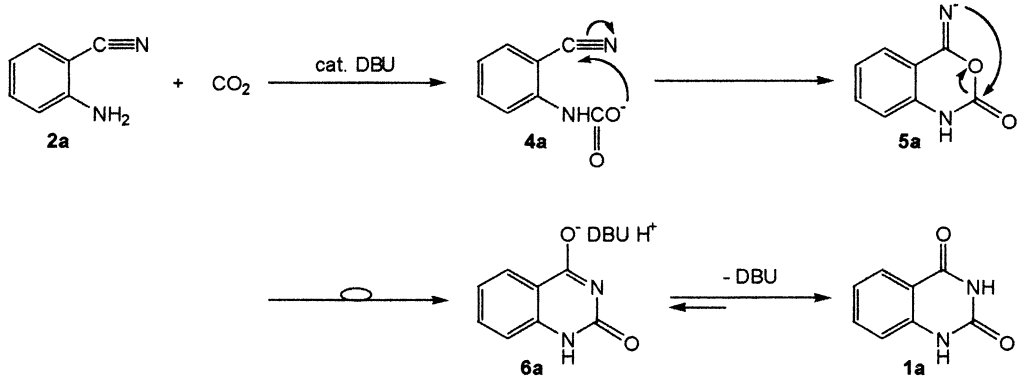


Figure 2. A plausible reaction pathway.

toluene (100 mL) and diethyl ether (100 mL). 1*H*-Quinazoline-2,4-dione (**1a**) was obtained in a 97% yield (1.57 g). 1*H*-Quinazoline-2,4-dione (**1a**). Mp>300°C (>350°C[11]); IR (KBr) 3255, 3055, 1705 cm^{-1}; ^1H 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.

4.2.1. 6,7-Dimethoxy-1*H*-quinazoline-2,4-dione (1b). Mp>300°C; IR (KBr) 3470, 1710 cm^{-1}; ^1H 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.

4.2.2. 6-Nitro-1*H*-quinazoline-2,4-dione (1c). Mp> 300°C; IR (KBr) 3455, 1680 cm^{-1}; ^1H 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.

4.2.3. 8-Bromo-6-nitro-1*H*-quinazoline-2,4-dione (1d). Mp>300°C; IR (KBr) 3175, 3080, 1700 cm^{-1}; ^1H 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.

4.2.4. Xanthine (1e). Mp>300°C (decomposition on heating without melting and with partial sublimation[12]); IR (KBr) 3005, 1705 cm^{-1}; ^1H 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.

4.3. General procedure for synthesis of 1*H*-quinazoline-2,4-dione (1a) in the presence of catalytic amount of DBU

In a 100 mL stainless steel autoclave, 2-aminobenzonitrile (**2a**) (1.18 g, 10 mmol), DBU (0.075 mL, 0.50 mmol), and DMF (20 mL) was placed with a magnetic stirring bar under an argon atmosphere. The autoclave was then flushed three times with carbon dioxide and finally charged with carbon dioxide at 10 atm at 20°C. The reaction was carried out at 80°C for 24 h with vigorous stirring. After cooling down and evacuation of carbon dioxide, the resulting mixture was then poured into 1 N HCl (200 mL), and the solid that deposited was washed with toluene (100 mL) and *t*-butyl methyl ether (100 mL). 1*H*-Quinazoline-2,4-dione (**1a**) was obtained in a 91% yield (1.48 g).

4.3.1. 6-Chloro-1*H*-quinazoline-2,4-dione (1f). Mp> 300°C; IR (KBr) 3200, 3060, 1745, 1715 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 7.16 (d, J=9 Hz, 1H), 7.64 (d, J=9 Hz, 1H), 7.78 (s, 1H), 11.24 (s, 1H), 11.41 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 115.7, 117.5, 125.9, 126.2, 134.7, 139.7, 150.0, 161.8; MS (*m/z*, %) 196 (M^+, 100), 153 (73), 125 (26); exact MS calcd for $C_8H_5ClN_2O_2$: 196.0040. Found: 196.0037.

4.3.2. 7-Chloro-1*H*-quinazoline-2,4-dione (1g). Mp> 300°C; IR (KBr) 3305, 3055, 1745, 1685 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 7.17–7.19 (m, 2H), 7.85 (d, J=9 Hz, 1H), 11.24 (s, 1H), 11.36 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 113.3, 114.7, 122.4, 129.0, 139.3, 141.9, 150.1, 162.0; MS (*m/z*, %) 196 (M^+, 100), 153 (91), 126 (49); exact MS calcd for $C_8H_5ClN_2O_2$: 196.0040. Found: 196.0036.

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