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The simple solvent-free synthesis of 1*H*-quinazoline-2,4-diones using supercritical carbon dioxide and catalytic amount of base

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Abstract—Only supercritical carbon dioxide ($scCO_2$) as a reactant and a solvent, and catalytic amount of base (DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), Dabco® (1,4-diazabicyclo[2.2.2]octane), and triethylamine) afforded 1*H*-quinazoline-2,4-diones in good to excellent yields from 2-aminobenzonitriles. 6,7-Dimethoxy-1*H*-quinazoline-2,4-dione, which is a key intermediate of medicines (Prazosin, Bunazosin, and Doxazosin) was synthesized successfully in a 97% yield, using 0.1 equiv of DBU under $scCO_2$ (10 MPa) at 80 °C.

Substituted 1*H*-quinazoline-2,4-diones **1** have been interesting for their biological activities. For example, 6,7-dimethoxy-1*H*-quinazoline-2,4-dione (**1b**) is a key intermediate for the production of the following medicines (Prazosin (Minipress®),[1] Bunazosin (Detantol®),[2] and Doxazosin (Cardenalin®)[3]) (Fig. 1). These medicines, which are effective α_1-adrenergic blocker, are useful for antihypertensives. 7-Chloro-1*H*-quinazoline-2,4-diones (**1d**) is also a key intermediate of medicines (FK 366 (Zenarestat®) and KF31327). FK 366 (Zenarestat®)

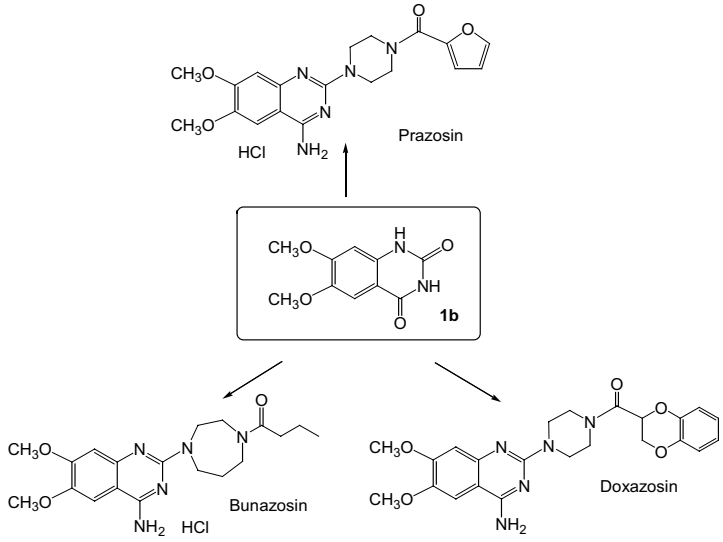

Figure 1. 6,7-Dimethoxy-1*H*-quinazoline-2,4-dione (**1b**) is a key intermediate of Prazosin (Minipress®), Bunazosin (Detantol®), and Doxazosin (Cardenalin®).

Keywords: Supercritical carbon dioxide; Carbonylation; Cyclization; Quinazolines; Quinazolidinones; DBU.
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showed the effect for an aldose reductase inhibitor, and was produced for a remedy of complications of diabetes mellitus,[4a,b] and KF31327 was developed as a heart disease remedy and an impotence medicine.[5]

The conventional syntheses of **1** are carried out by anthranilic acid with urea,[6a,b] anthranilamide with phosgene,[7] and anthranilic acid with potassium cyanate[8] or chlorosulfonyl isocyanate.[9] However, these synthetic methods are considerably limited because of high toxicity of the reagents or the use of drastic conditions.

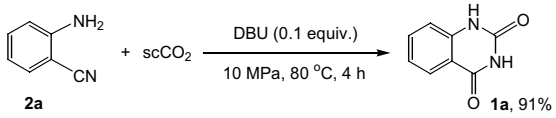
We recently reported a convenient synthesis of 1*H*-quinazoline-2,4-diones **1** from 2-aminobenzonitriles **2** by the chemical fixation of carbon dioxide under mild conditions (0.1 MPa, 20 °C) in the presence of an excess amount of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or DBN (1,5-diazabicyclo[4.3.0]non-5-ene) using DMF as a solvent.[10a,b] Furthermore, we also found that a catalytic amount of DBU or DBN has the exceptional ability for the chemical fixation of carbon dioxide to give **1** in excellent yields under 1.0 MPa at 80 °C in DMF or DMSO.[11] However, these reactions need DMF or DMSO as an organic solvent.

Carbon dioxide is 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 processes for chemical fixation almost remain significant synthetic challenges. Also, use of supercritical carbon dioxide as a substitution for organic solvents is of great important, because of both for the toxicity for human and the environmental problems of organic solvents.[12a–c]

Therefore, if solvent-free synthesis of substituted 1*H*-quinazoline-2,4-diones **1** from 2-aminobenzonitriles **2** using only supercritical carbon dioxide and catalytic amount of base is established, it would be one of the ideal organic reactions.

With our goal in mind, we now developed a new simple solvent-free synthesis of substituted 1*H*-quinazoline-2,4-diones **1**, which include medicine intermediates, using supercritical carbon dioxide as a reactant and a solvent, and catalytic amount of base (DBU, DBN, Dabco® (1,4-diazabicyclo[2.2.2]octane), and triethylamine).[13]

At the outset, our trial showed a successful result of synthesis of 1*H*-quinazoline-2,4-dione (**1a**) with supercritical carbon dioxide. 2-Aminobenzonitrile (**2a**) easily reacted with $scCO_2$ at 10 MPa, 80 °C for 4 h in the presence of DBU (0.1 equiv). Finally, 1*H*-quinazoline-2,4-dione (**1a**) was given in 91% yield (Scheme 1).[15]



Scheme 1.

Table 1. Effect of pressure and bases (0.1 equiv) for synthesis of **1a**

Entry	Pressure (MPa)	Base	Yield (%)
1	20[a]	DBU[b]	88
2	10[a]	DBU[b]	91
3	10[a]	DBU[b,c]	69
4	6.0	DBU[b]	89
5	3.0	DBU[b]	76
6	10[a]	DBN[d]	86
7	10[a]	Dabco[e]	89
8	10[a]	Et_3N	70
9	10[a]	Pyridine	0
10	10[a]	K_2CO_3	0
11	10[a]	None	0

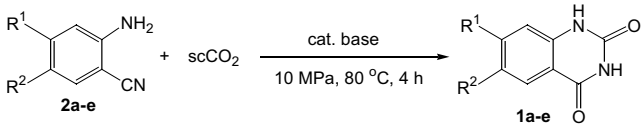
[a] Supercritical state of CO_2.
[b] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[c] DBU (0.05 equiv) was used.
[d] 1,5-Diazabicyclo[4.3.0]non-5-ene.
[e] 1,4-Diazabicyclo[2.2.2]octane.

A variety of conditions of pressure and bases was investigated for the synthesis of **1a** under solvent-free at 80 °C for 4 h (Table 1). Under supercritical state of CO_2 (10.0–20.0 MPa) and 6.0 MPa of CO_2, 1*H*-quinazoline-2,4-dione (**1a**) was given in excellent yields (88–91%) in the presence of catalytic amount of DBU (0.1 equiv) (entries 1, 2, and 4). However, using a less amount of DBU (0.05 equiv) and low pressure of CO_2 (3.0 MPa) lowered the yield of **1a** (entries 3 and 5).

DBU, DBN, and Dabco® as bases gave the best results of synthesis of **1a** (91%, 86%, and 89%, respectively) (entries 2, 6, and 7). Surprisingly, triethylamine afforded 1*H*-quinazoline-2,4-dione (**1a**) in fairly good yield (70%) (entry 8). However, other bases (pyridine, K_2CO_3, and none) did not give the product (**1a**) at all (entries 9–11).

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.[17a–d]

Several 1*H*-quinazoline-2,4-diones (**1a–d**), which include the key intermediates (**1b** and **1d**) of medicines, were synthesized similarly in good to excellent yields, from the corresponding 2-aminobenzonitriles (**2a–d**) with carbon dioxide in the presence of 0.1–0.2 equiv of DBU or triethylamine under supercritical CO_2 conditions (10 MPa, 80 °C) (Scheme 2). However, 6-nitro-1*H*-qui-



Scheme 2. 1a, R^1 = H, R^2 = H, DBU (0.1 equiv): 91%, Et_3N (0.1 equiv): 70%; **1b**, R^1 = CH_3O, R^2 = CH_3O, DBU (0.1 equiv): 97%; **1c**, R^1 = H, R^2 = Cl, DBU (0.1 equiv): 54%, DBU (0.2 equiv): 96%, Et_3N (0.2 equiv): 86%; **1d**, R^1 = Cl, R^2 = H, DBU (0.1 equiv): 64%, DBU (0.2 equiv): 67%; **1e**, R^1 = H, R^2 = NO_2, DBU (0.1 equiv): 0%, DBU (0.5 equiv): ca. 20%.

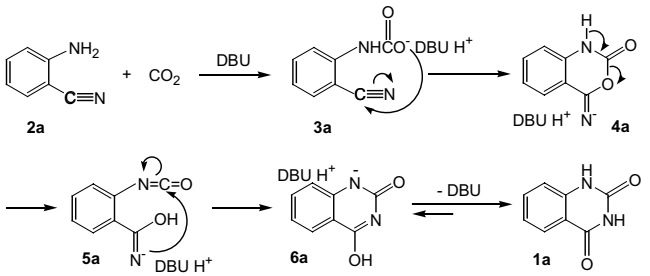


Figure 2. A plausible reaction pathway.

nazoline-2,4-diones (**1e**) was obtained from 2-amino-5-nitro-benzonitrile (**2e**) in only ca. 20% yield[18] even using 0.5 equiv of DBU, because of low basicity of **2e**.

Figure 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 in the presence of catalytic DBU. Then, nucleophilic cyclization of **3a** into **4a**, followed by rearrangement of **4a** by the way of isocyanate intermediate **5a**, gives **6a**. Finally, by the stabilization of **6a**, the final product (**1a**) is afforded. In this reaction system, formation of isocyanate intermediate **5a** assisted by *o*-cyano group seems to be important. An industrial urea synthesis in which an isocyanate is an intermediate, is performed under high temperature conditions.[19]

In conclusion, a new simple solvent-free synthesis of substituted 1*H*-quinazoline-2,4-diones **1**, which include medicine intermediates (Prazosin (Minipress®), Bunazosin (Detantol®), Doxazosin (Cardenalin®), FK 366 (Zenarestat®), and KF31327) from 2-aminobenzonitriles was developed, using only supercritical carbon dioxide as a reactant and a solvent, and catalytic amount of base (DBU, DBN, Dabco®, and triethylamine). The present reaction seems to be one of the ideal synthetic reactions.

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15. General procedure for synthesis of 1*H*-quinazoline-2,4-dione (**1a**) using $scCO_2$ and catalytic amount of DBU. Into a 50 mL stainless steel autoclave, 2-aminobenzonitrile (**2a**) (1.18 g, 10 mmol) and DBU (0.15 mL, 1.0 mmol) were placed with a magnetic stirring bar. The autoclave was finally charged with carbon dioxide at 10 MPa using $scCO_2$ reaction system (JASCO Corp.). The reaction was carried out at 10 MPa, 80 °C for 4 h with stirring. After evacuation of carbon dioxide and cooling down, the resulting solid was then poured into 1 N HCl (100 mL) and washed with water (100 mL) and *t*-butyl methyl ether (100 mL). 1*H*-Quinazoline-2,4-dione (**1a**) was obtained in a 91% yield (1.47 g). 1*H*-Quinazoline-2,4-dione (**1a**): mp > 300 °C (>350 °C[16]); IR (KBr) 3255, 3055, 1705 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) 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) 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.
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