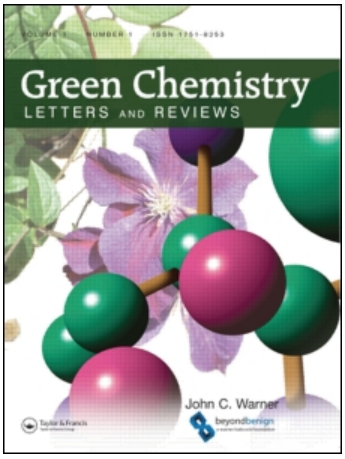

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Cesium carbonate catalyzed efficient synthesis of quinazoline-2,4(1*H*,3*H*)-diones using carbon dioxide and 2-aminobenzonitriles

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ORIGINAL ARTICLE

Cesium carbonate catalyzed efficient synthesis of quinazoline-2,4(1*H*,3*H*)-diones using carbon dioxide and 2-aminobenzonitriles

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An efficient protocol for the synthesis of quinazoline-2,4(1*H*,3*H*)-diones derivatives from 2-aminobenzonitriles with carbon dioxide using catalytic amount of cesium carbonate has been developed. 6,7-Dimethoxyquinazoline-2,4(1*H*,3*H*)-dione, which is one of the key intermediate for the synthesis of several drugs (Prazosin, Bunazosin and Doxazosin) was synthesized. The effect of different reaction parameters like influences of bases, solvent, temperature, CO_2 pressure and reaction time were investigated for the title reaction.

Keywords: cesium carbonate; carbon dioxide; carbonylation; cyclization; quinazoline-2,4(1H,3H)-diones derivatives

Introduction

"Carbon dioxide" (CO_2) is a cheap, abundant natural carbon source and one of the important C_1 building blocks for the synthesis of several organic compounds. The synthesis of CO_2-based industrially important chemicals has attracted much interest in recent years in view of the sustainable chemistry and "green chemistry" concept (*1,2*). Quinazoline-2,4(1*H*,3*H*)-diones have emerged as preeminent classes of organic compounds, which holds applications due to the wide range of biological properties. Hence, they are important intermediates in the pharmaceutical industry as key building blocks in the synthesis of FK 366 (Zenarestat) and KF 31327 molecules (Scheme 1). FK 366 (Zenarestat) functions as an aldose reductase inhibitor and was produced as a remedy for complications of diabetes mellitus (*3,4*) and KF 31327 was developed as a remedial drug for heart disease and as an impotence medicine (*5*). The 6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione derivative is useful as a building block in the synthesis of alpha adrenergic receptor antagonists such as Prazosin (Minipress®) (*6*), Bunazosin (Detantol®) (*7*) and Doxazosin (Cardenalin®) (*8*) (Scheme 1), and which are useful as antihypertensive agents.

Numerous synthetic methodologies exist for the preparation of quinazoline-2,4(1*H*,3*H*)-diones from anthranilic acid and urea (*9,10*) anthranilamide and phosgene (*11*) and anthranilic acid and potassium cyanate (*12*) or chlorosulfonyl isocyanate (*13*). However, the scope of existing methodologies for the preparation of quinazoline-2,4(1*H*,3*H*)-diones is limited by the requirement for specialized reagents, and operational complexity due to the use of either toxic or cumbersome reagents like phosgene. Few efforts were made to replace toxic reagents using incorporation of CO_2 into quinazoline-2,4(1*H*,3*H*)-diones derivatives. Mizuno and co-workers reported for the first time the synthesis of quinazoline-2,4(1*H*,3*H*)-diones by reacting 2-aminobenzonitrile with CO_2 in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (*14–18*). The use of DBU is disadvantageous due to the problems associated with handling such as the hygroscopic nature, high viscosity, and tedious rework procedures. Hence, considering the economical value of the quinazoline-2,4(1*H*,3*H*)-diones derivatives there is still a need to develop simple protocols which can minimize the number of unit operations and waste streams. Recently, it has been observed that Cs^+ compounds are active for the catalytic activation of CO_2, amines and alcohols which gives selective formation of symmetric/asymmetric ureas and carbamates derivatives (*19–21*). Hence, in the framework of our effort in developing new methods based on CO_2 as a reagent (*22–27*), we herein report a cesium carbonate (Cs_2CO_3) catalyzed efficient synthesis of quinazoline-2,4(1*H*,3*H*)-diones using CO_2 and 2-aminobenzonitriles (Scheme 2). Cs_2CO_3 showed remarkable activity and the catalytic system was applicable to a wide variety of substituted

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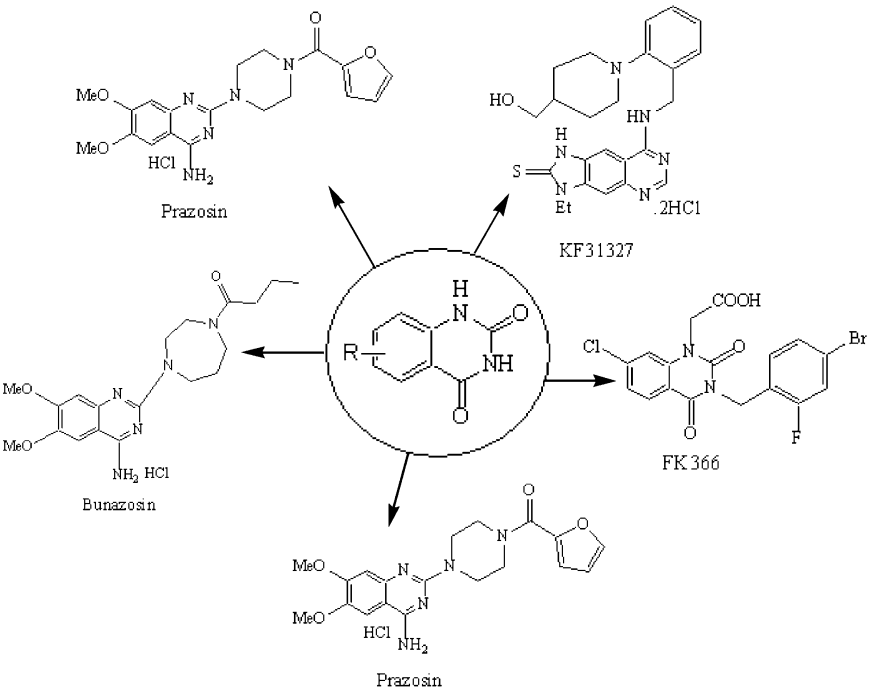
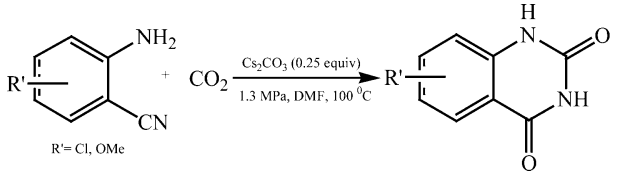


Scheme 1. Quinazoline-2,4(1*H*,3*H*)-diones derivative; a key intermediate for the synthesis of FK 366, KF 31327, Prazosin, Bunazosin, and Doxazosin.

2-aminobenzonitriles with different steric and electronic properties.

Results and discussion

The present work aims at the development of an efficient protocol for the synthesis of quinazoline-2,4(1*H*,3*H*)-diones derivatives from 2-aminobenzonitriles using CO_2. Initially the reaction of 2-aminobenzonitrile with CO_2 to quinazoline-2,4(1*H*,3*H*)-diones was chosen as a model reaction for the exploration of suitable catalyst for this transformation. It is well known that bases are effective catalysts for CO_2-based transformations; hence, various organic and inorganic bases like K_2CO_3, Na_2CO_3, KF, *t*-BuOK, KOH and Et_3N were tested for this reaction. Typical results are shown in Table 1. It was found that in the absence of a base a reaction did not proceed to desired products (Table 1, entry 1). It was also observed that Na_2CO_3 and Et_3N were ineffective catalysts (entries 3 and 6). Whereas, other bases like K_2CO_3, KF, *t*-BuOK and KOH were found to give yield of quinazoline-2,4(1*H*,3*H*)-diones (**2a**) in the range of 35–55%. In comparison, catalytic amounts of Cs_2CO_3 were found to be effective providing an excellent yield (94%) of **2a** (entry 10). The probable reason may be due to the softness of the cesium



Scheme 2. Synthesis of various quinazoline-2,4(1*H*,3*H*)-diones from substituted 2-aminobenzonitriles and carbon dioxide.

Table 1. Influences of bases on the synthesis of quinazoline-2,4(1*H*,3*H*)-diones.[a]

Entry	Base	Base (equiv.)	Yield[b] (%)
1	Without base	0	0
2	K_2CO_3	0.25	35
3	Na_2CO_3	0.25	0
4	KF	0.25	40
5	*t*-BuOK	0.25	33
6	Et_3N	0.25	0
7	KOH	0.25	55
8	Cs_2CO_3	1	94
9	Cs_2CO_3	0.5	94
10	Cs_2CO_3	0.25	94
11	Cs_2CO_3	0.12	83

[a]Reaction condition: 2-aminobenzonitrile (20 mmol), DMF (20 ml), CO_2 (1.3 MPa), 4 h at 100°C.
[b]Isolated yield (%).

cation. This softness makes Cs_2CO_3 rather soluble in organic solvent such as DMF and alcohol (*28*). The reaction using different catalytic concentrations of Cs_2CO_3 was carried out and typical results are shown in Table 1 (entries 8–11). It was observed that the yield of **2a** was almost constant at 1, 0.5, 0.25 equiv. of Cs_2CO_3. However, lower amounts of Cs_2CO_3 (0.12 equiv.) give lower yield of **2a** (entry 11).

Thus using Cs_2CO_3 as the choice of base catalyst, we examined the influences of other reaction parameters such as solvent, temperature, pressure and time to evaluate the scope and limitation of the current catalyst system (Table 2). The effect of various solvents on the reaction system was investigated (entries 1–5). It was observed that THF and non-polar solvent like toluene were found to be ineffective under the present condition, whereas, polar solvent like ethanol and water were found to give only (15–5%) yield of quinazoline-2,4(1*H*,3*H*)-diones. In comparison anhydrous DMF was found to be the best solvent providing an excellent yield (94%) of **2a** (entry 5). CO_2 and Cs_2CO_3 have higher solubility in DMF compared to ethanol, which effectively results in higher yield of the product. Furthermore, both CO_2 and Cs_2CO_3 have higher solubility in water, but the reactants used for the reaction are insoluble in water which result in lower yield of the product.

The influence of temperature on the yield of quinazoline-2,4(1*H*,3*H*)-diones was investigated and the results obtained are shown in Table 2 (entries 6–8) and it was observed that the temperature had a pronounced positive effect on the quinazoline-2,4(1*H*,3*H*)-diones synthesis. When the reaction was carried out at 80°C, the reaction did not occur. However, with an increase in the reaction temperature from 100 to 120°C the yield increased to 94–95% after 4 h. Considering the above experimental conditions, the optimal temperature was found to be 100°C. As shown in Table 2 (entries 9–11), a remarkable feature of the reaction is that the CO_2 pressure showed no effect on the quinazoline-2,4(1*H*,3*H*)-dione yield in the CO_2 pressure range of 1.3 MPa–2.7 MPa. A higher yield of **2a** was obtained at a low pressure of 1.3 MPa (entry 11). Indeed, the base catalyst efficiently operated at 1.3 MPa. Even at pressures below 1 MPa, the decline in activity was marginal (entry 12). The effect of reaction time was also optimized and it was observed that the Cs_2CO_3 exhibits high activity even at short reaction time as shown in entries 13–16. It can be seen that almost quantitative yield of **2a** (94%) was achieved within

Table 2. Effect of various reaction parameters on quinazoline-2,4(1*H*,3*H*)-diones synthesis from 2-aminobenzonitrile and CO_2.[a]

Entry	Catalyst	Solvent	Temperature(°C)	CO_2 pressure (Mpa)	Time (h)	Yield[b] (%)
Effect of solvent						
1	Cs_2CO_3	Toluene	100	1.3	4	0
2	Cs_2CO_3	Ethanol	100	1.3	4	15
3	Cs_2CO_3	THF	100	1.3	4	0
4	Cs_2CO_3	Water	100	1.3	4	5
5	Cs_2CO_3	DMF	100	1.3	4	94
Effect of temperature						
6	Cs_2CO_3	DMF	120	1.3	4	95
7	Cs_2CO_3	DMF	100	1.3	4	94
8	Cs_2CO_3	DMF	80	1.3	4	0
Effect of pressure						
9	Cs_2CO_3	DMF	100	2.7	4	93
10	Cs_2CO_3	DMF	100	1.8	4	94
11	Cs_2CO_3	DMF	100	1.3	4	94
12	Cs_2CO_3	DMF	100	1	4	80
Effect of time						
13	Cs_2CO_3	DMF	100	1.3	5	94
14	Cs_2CO_3	DMF	100	1.3	4	94
15	Cs_2CO_3	DMF	100	1.3	3	75
16	Cs_2CO_3	DMF	100	1.3	1	10

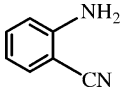
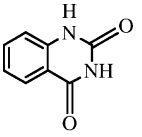
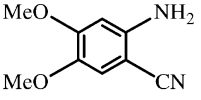
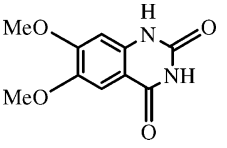
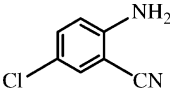
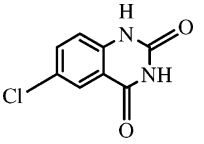
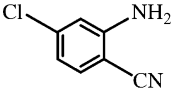
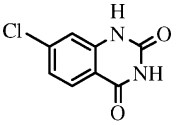
[a]Reaction condition: 2-aminobenzonitrile (20 mmol), catalyst (0.25 equiv.), solvent (20 ml).
[b]Isolated yield (%).

4 h (entry 14). No further increase in the yield of **2a** was observed for longer reaction time above 4 h. Therefore, the reaction time of 4 h is suitable for the synthesis of **2a** quantitative at 100°C.

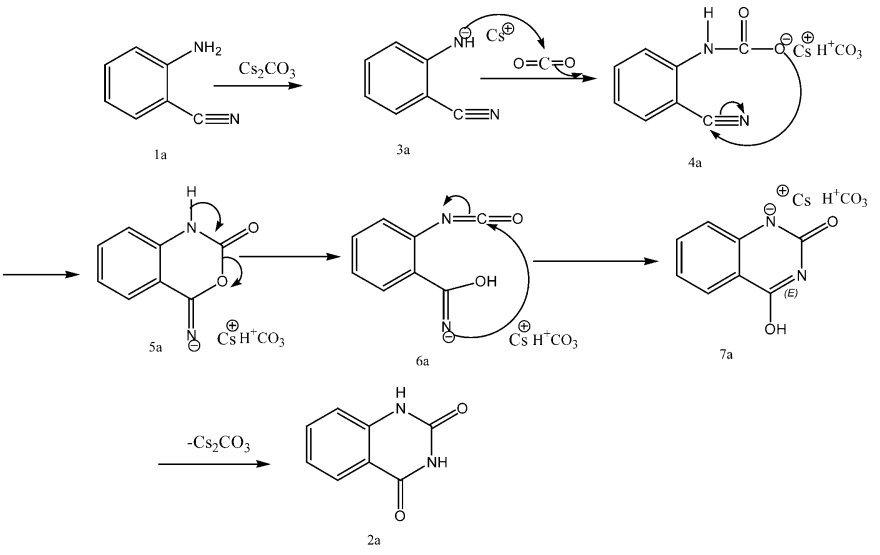
Under the optimized reaction parameters the syntheses of various quinazoline-2,4(1*H*,3*H*)-diones **2a**–**2d** from various substituted 2-aminobenzonitrile having different steric and electronic properties were carried out (Table 3, entries 1–4). The reaction of 2-aminobenzonitrile with CO_2 provided 94% yield of quinazoline-2,4(1*H*,3*H*)-dione under mild reaction conditions (entry 1). 2-Amino 4,5 dimethoxybenzonitrile (**1b**) was effectively reacted with CO_2 under the present conditions providing an excellent yield up to 88% of 6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione (**2b**) (entry 2). Although we know that **2b** is a key intermediate for the synthesis of Prazosin (Minipress), Bunazosin (Detantol) and Doxazosin (Cardenalin), to check the generality of the procedure the system was extended to various 2-amino-5-Cl-benzonitrile (**1c**) and 2-amino-4-Cl-benzonitrile (**1d**), and it was observed that **1c** reacted smoothly with CO_2 providing excellent yield up to 80% (entry 3). Whereas **1d** provided only 51% yield of 7-chloroquinazoline-2,4(1*H*,3*H*)-dione (**2d**) under the present experimental conditions (entry 4).

Scheme 3 showed a proposed mechanism for Cs_2CO_3 promoted **2a** synthesis in the presence of 2-aminobenzonitrile (**1a**) and CO_2. The amide (**3a**) which is generated in situ, can be formed by the reaction of **1a** with Cs_2CO_3 in anhydrous DMF. The amide is free from the conjugate cesium ion; it is a

Table 3. Synthesis of various quinazoline-2,4(1*H*,3*H*)-diones **2a**–**2d**.[a]

Entry	Reactant	Product	Yield[b] (%)
1	 **1a**	 **2a**	94
2	 **1b**		88
3	 **1c**	 **2c**	80
4	 **1d**	 **2d**	51

[a]Reaction condition: reactant (20 mmol), Cs_2CO_3 (0.25 equiv.), CO_2 (1.3 MPa), DMF (20 ml), 4 h at 100°C.
[b]Isolated yield (%).



Scheme 3. Reaction mechanism.

"naked anion," which renders it more nucleophilic. The amide (**3a**) then rapidly reacts with CO_2, giving rise to the carbamate ester (**4a**) (*21*). Then nucleophilic cyclization of (**4a**) into (**5a**), followed by the rearrangement of (**5a**) by way of the isocyanate intermediate (**6a**) gives (**7a**). Finally, stabilization of (**7a**) gives the final product (**2a**). The formation of the isocynate intermediate (**6a**) assisted by the *o*-cyano group appears to be of importance (*18*).

Conclusion

Several important features were demonstrated in this study. Firstly, an efficient protocol for the synthesis of quinazoline-2,4(1*H*,3*H*)-diones using Cs_2CO_3. Secondly, considering the economical value of the quinazoline-2,4(1*H*,3*H*)-diones derivatives we developed a new methodology which minimizes the number of unit operations and waste streams. Thirdly, solid base catalyst like Cs_2CO_3 is very good to handle in unit operation. Fourthly, the system works well with a wide variety of 2-aminobenzonitriles with different steric and electronic properties.

Experimental section

General

All chemicals were procured from firms of repute. Cs_2CO_3 was made available from Lancaster. Various substrate of 2-aminobenzonitrile were purchased from Sigma-Aldrich. DMF was purchased from S. D. Fine Chem. Ltd. All the chemicals were used as received without any further purification. IR spectra were recorded on FT-IR Perkin Elmer using KBr. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian-300 and 75 MHz NMR spectrometer using TMS as an internal standard. Mass spectra were recorded on Finnigan Mass Spectrometer (MAT XL95).

Typical experimental procedure for the synthesis of quinazoline-2,4(1H,3H)-diones

A mixture of 2-amiobenzonitrile (20 mmol) and Cs_2CO_3 (0.25 equiv.) in 20 ml of DMF was placed in a 100 ml stainless steel autoclave. The autoclave was flushed with CO_2 and then 1.3 MPa of CO_2 was taken. The reaction mixture was stirred at 100°C for 4 h. After the completion of the reaction, the autoclave was cooled to room temperature and the reaction mixture was poured into water. The resulting precipitate was filtered through a Buckner funnel, washed with *t*-BuOMe (50 ml) and dried at 100°C under vacuum. Isolated products were characterized by IR, ^{1}H NMR, ^{13}C NMR (Varian 300 MHz, 75 MHz) and MS.

Spectral data for selected products

Table 3, entry ***2a***. IR (KBr): 3252, 3056, 2840, 1720, 1704, 1668, 1621, 1444, 756 cm^{-1}. ^{1}H NMR (300 MHz, DMSO, 25°C, TMS): $\delta = 7.14$–7.17 (m, 2H, 2 CH), 7.60 (t, $J = 7.5$ Hz, 1H, CH), 7.87 (d, $J = 7.8$ Hz, 1H, CH), 11.19 (s, 2H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25°C, TMS): $\delta = 114.35$, 115.33, 122.32, 126.96, 134.95, 140.88, 150.34, 162.86 ppm. MS: $m/z = 163.02$ (M^+), 146.0, 90.0.

Table 3, entry ***2b***. IR (KBr): 3467, 3329, 3290, 1706, 1650, 1626, 1465, 1426, 1265, 1101 cm^{-1}. ^{1}H NMR (300 MHz, DMSO, 25°C, TMS); $\delta = 3.78$ (s,

3H, CH_3), 3.81 (s, 3H, CH_3), 6.67 (s, 1H, CH), 7.25 (s, 1H, CH), 11.03 (s, 2H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25°C, TMS): $\delta = 55.68$, 55.78, 97.75, 106.19, 107.12, 136.55, 145.10, 150.42, 154.90, 162.43 ppm. MS: $m/z = 223.0$ (M^+), 154.9, 91.0, 45.7.

Table 3, entry ***2c***. IR (KBr): 3196, 3060, 1736, 1715, 1665, 1483, 1429, 1285, 829 cm^{-1} ^1H NMR (300 MHz, DMSO, 25°C, TMS): $\delta = 7.14$ (d, $J = 8.7$ Hz, 1H, CH), 7.62 (d, $J = 8.29$ Hz, 1H, CH), 7.76 (s, 1H, CH), 11.34 (s, 2H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25°C, TMS): $\delta = 115.73$, 117.47, 125.87, 126.26, 134.72, 139.69, 150.01, 161.80 ppm. MS: $m/z = 196.9$ (M^+), 179.9, 123.9, 91.0, 45.8.

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