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Chemical fixation of CO_2: efficient synthesis of quinazoline-2,4(1*H*, 3*H*)-diones catalyzed by guanidines under solvent-free conditions

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ABSTRACT

Guanidines were proved to be efficient catalysts for the chemical fixation of carbon dioxide with 2-aminobenzonitriles under solvent-free conditions. Notably, the catalysts with low loading worked well for a variety of 2-aminobenzonitriles. As a result, quinazoline-2,4(1*H*, 3*H*)-diones by employing present protocol were obtained in good yields under mild conditions. This process represents an alternative approach for the greener chemical fixation of CO_2 to afford valuable compounds.

1. Introduction

In recent years, quinazoline-2,4(1*H*, 3*H*)-diones and their derivatives, such as 7-chloroquinazoline-2,4(1*H*, 3*H*)-dione and 6,7-dimethoxy-quinazoline-2,4(1*H*, 3*H*)-dione, have drawn much attention and interest due to their wide range of biological and pharmacological activities.[1–6] Reactions of anthranilic acid with urea,[7] anthranilamide with phosgene[8] or anthranilic acid with potassium cyanate[9] or chlorosulfonyl isocyanate[10] are considered as conventional synthetic routes to quinazoline-2,4(1*H*, 3*H*)-diones. Recently, alternative methods were also developed to minimize the use of high toxic reagents and/or to avoid harsh reaction conditions. In this context, greener synthetic methodologies covering solid phase synthetic approachs,[11] microwave-assisted synthesis[12] or metal involved methods[13] have been available in the literature. Nevertheless, the cyanate reagent is still needed for the preparation of quinazoline-2,4(1*H*, 3*H*)-diones derivatives by utilizing those improved processes. Therefore, the development of efficient and greener synthetic strategy remains challenging.

Naturally abundant, inexpensive, non-flammable and non-toxic carbon dioxide is regarded as an attractive and economical C1 building block in organic synthesis to produce useful compounds and material.[14] On the other hand, chemical fixation of CO_2 would be of great significance from the viewpoint of both utilization of carbon resources and the increasing concern of the environment. Recently, a promising strategy for the synthesis of quinazoline-2,4-(1*H*, 3*H*)-diones starting from CO_2 was proposed by Mizuno et al.,[15] in which stoichiometric organic base DBU (1,8-diazabicyclo [5.4.0] undec-7-ene) is required. In this context, substantial progress was achieved by developing catalytic process,[16a] solvent-free protocol,[16b,c] or heterogeneous catalysis for easy separation.[16d,e] Development of more efficient catalysts could be desirable and challenging in order to decrease catalyst loading and shorten reaction time as well as facilitate product separation.

Organic guanidines, which are categorized as organic superbases with ease of structural modification,[17] are efficient organic catalysts for the types of base induced reactions in organic synthesis.[18] Particularly, guanidines could interact with CO_2 through a kinetically reversible way, leading to CO_2 fixation.[19]

As our continuous interest in chemical fixation of CO_2,[20] we developed an efficient approach for the synthesis quinazoline-2,4(1*H*, 3*H*)-diones from CO_2 and 2-aminobenzonitriles catalyzed by low amounts of organic guanidines without the need of any additional solvent. In this regard, several guanidines were proved to be effective for this process. Among the tested catalysts, the simplest guanidine, i.e., 1,1,3,3-tetramethylguanidine (TMG) exhibited high catalytic activity.

2. Results and discussion

The exploratory experiments were started by testing this protocol and screening the reaction conditions using 2-aminobenzonitrile (**1a**) as the benchmark substrate, as depicted in Scheme 1. Various organic bases were initially tested for the

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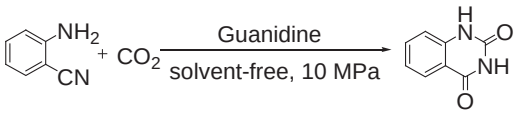
reaction of incorporating CO_2 into 2-aminobenzonitrile. As easily seen from Table 1, the coupling reaction of **1a**/CO_2 did not occur at all in the absence of any catalyst (entry 1). Moreover, several examined organic bases, such as hexamethylenetetramine (HMT) and diethylenetriamine (DETA), were also found to be inactive at 80 °C (entry 2), presumably being ascribed to lack of enough basicity. To our delight, the organic guanidine, e.g., *N*-(1,3-dimethylimidazolidin-2-ylidene) butan-1-amine (**G1**, Scheme 2) was effective for the reaction and a 25% isolated yield of quinazoline-2,4(1*H*, 3*H*)-dione (**2a**) was attained (entry 3). As anticipated, the reaction was further facilitated by increasing in the reaction temperature (entries 3–5). Excellent **2a** yield was obtained at 120 °C under solvent-free conditions. It is also worth mentioning that the organic guanidines, e.g., TMG, **G1**–**G3** and 1,5,7-triazabicyclo [4.4.0] dec-1-ene (TBD) used in this study (Scheme 2) gave excellent catalytic activity under the identical reaction conditions (entries 5–9). More interestingly, TMG showed the highest catalytic performance at the catalyst amount as low as 2 mmol % relative to **1a** (entries 10–14), being presumably attributed to influence of basicity and steric effect. As a consequence, the simplest and easily available guanidine, viz. TMG was chosen as the catalyst for further investigation.



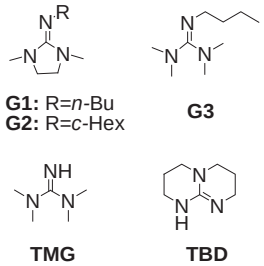
1a **2a**

Scheme 1. Guanidine-catalyzed reaction of 2-aminobenzonitrile **1a** and CO_2.

Table 1
Screening bases[a]

Entry	Cat.	Amount of Cat. (equiv.)	*T* (°C)	Isolated yield (%)
1[b]	0	0	80	0
2[b,c]	**HMT**	0.1	80	0
3	**G1**	0.1	80	25
4	**G1**	0.1	100	32
5	**G1**	0.1	120	88
6	**G2**	0.1	120	89
7	**G3**	0.1	120	86
8	**TMG**	0.1	120	87
9	**TBD**	0.1	120	81
10	**G1**	0.02	120	34
11	**G2**	0.02	120	36
12	**G3**	0.02	120	27
13	**TMG**	0.02	120	82
14	**TBD**	0.02	120	26

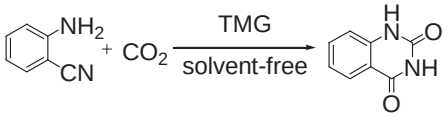
[a] Reaction conditions: **1a** (0.591 g, 5 mmol), CO_2 10 MPa, 4 h.
[b] **1a** (0.1182 g, 1 mmol), 2 mL of DMF (dimethyl formamide), 12 h.
[c] HMT: hexamethylenetetramine and other organic bases such as D301R (a kind of ion exchange resin, i.e., polystyrene with $N(CH_3)_2$ as a functional group, supplied from the Chemical Plant of Nankai University), PTA (1,3,5-triaza-7-phosphaadamantane), DETA (diethylenetriamine) also showed no catalytic activity under the identical reaction conditions (see the Supplementary data).



Scheme 2. Guanidines used in this study.

Subsequently, the effects of several reaction parameters were investigated as listed in Table 2. Interestingly, good yield of **2a** could be reached even with low catalyst loading (entry 4, Table 2). On the other hand, influence of the reaction time was examined. Satisfactory result could be also achieved within 1 h (entry 6), which is quite shorter in comparison with values in the literatures.[15,16] Whereas, more than 3 h is needed for almost full completion of the reaction (entries 3,7–9).

Table 2
Effect of reaction parameters on the reaction[a]



1a **2a**

Entry	TMG (equiv.)	P_{CO2} (MPa)	Time (h)	Isolated yield (%)
1	0.2	10	4	87
2	0.1	10	4	87
3	0.05	10	4	87
4	0.02	10	4	82
5	0.05	10	0.5	21
6	0.05	10	1	69
7	0.05	10	3	88
8	0.05	10	5	87
9	0.05	10	6	88

[a] Reaction conditions: **1a** (0.591 g, 5 mmol), 120 °C.

Shown in Figure 1 is the yield of the desired product as a function of CO_2 pressure in the reaction of CO_2 and **1a**. Obviously, **2a** yield is sensitive to CO_2 pressure. Although CO_2 pressure as low as 0.5 MPa also worked well, 10 MPa gave the maximum value. However, further increasing CO_2 pressure up to 16 MPa led to a decrease in yield. This is because excessive CO_2 may cause low concentration of the substrate and the catalyst, thus resulting in a low yield. Therefore, 10 MPa would be an appropriate operating pressure.

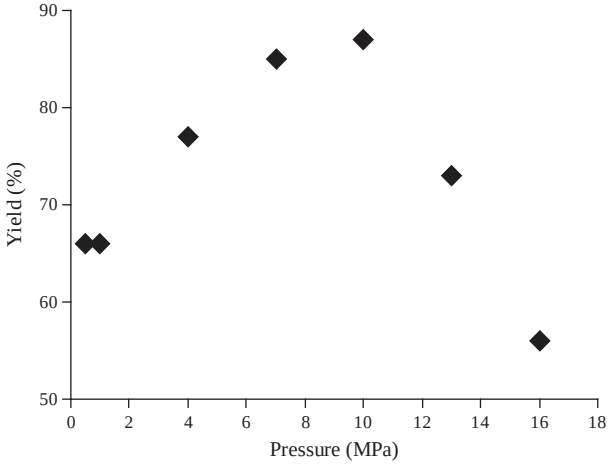
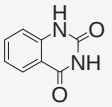
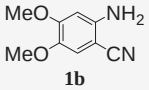
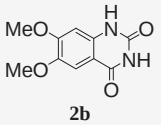
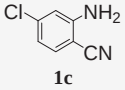
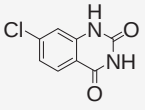
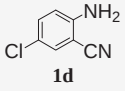
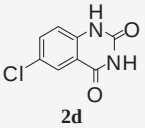
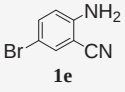
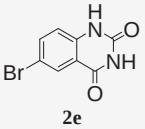
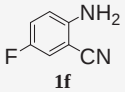
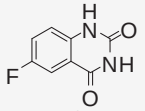
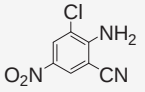
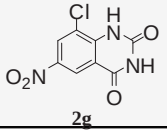


Figure 1. Plot of yield as a function of CO_2 pressure for the reaction of CO_2 and **1a**. Reaction conditions: **1a** (0.591 g, 5 mmol), TMG (29 mg, 0.25 mmol), 120 °C, 4 h.

To demonstrate the utility and generality of this approach to the synthesis of quinazoline-2,4(1*H*, 3*H*)-diones, we examined the reactions of various 2-aminobenzonitriles and CO_2 by performing the reaction under the identical conditions. A variety of 2-aminobenzonitriles bearing electron-withdrawing or electron-donating substituents were tested by employing TMG as the catalyst (Table 3). It was found that the catalyst worked well for

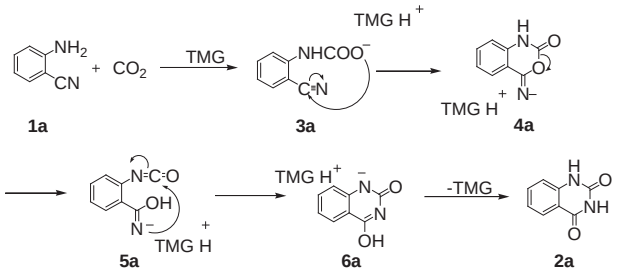
Table 3
Synthesis of various quinazoline-2,4(1*H*, 3*H*)-diones **2a–f**[a]

Entry	Substrate	Product	Isolated yield (%)
1	 **1a**	 **2a**	89
2	 **1b**	 **2b**	88
3	 **1c**	 **2c**	60
4	 **1d**	 **2d**	95
5	 **1e**	 **2e**	81
6	 **1f**	 **2f**	91
7	 **1g**	 **2g**	0

[a] Reaction conditions: subtrate (2 mmol), TMG (11.6 mg, 5 mmol %), CO_2 10 MPa, 120 °C, 4 h. Reactions were performed in a 25 mL stainless steel autoclave.

most of 2-aminobenzonitriles (**1a–f**) tested in this study to give the corresponding quinazoline-2,4(1*H*, 3*H*)-diones (**2a–f**) in excellent isolated yields (entries 1–6). The presence of electron-donating group has likely no influence on the reaction (entry 2). On the other hand, reactivity of *meta*-halogen substituted 2-aminobenzonitriles is found to follow the trend of Cl>F>Br (entries 4–6). Particularly, *para*-substituent **1c** showed less active compared with its *meta* counterpart **1d**, probably due to electron-withdrawing effect on the basicity. Indeed, 2-aminobenzonitrile **1g** bearing both an *m*-nitro and an *m*-halogen group failed to react with CO_2 forming the product **2g** even at reaction temperature as high as 140 °C.

On the basis of previous studies[15,16] and experimental results, a plausible mechanism for the TMG-catalyzed reaction of 2-aminobenzonitrile (**1a**) and CO_2 is proposed as depicted in Scheme 3. First of all, the carbonylation of **1a** with CO_2 generates the intermediate carbamate salt **3a** promoted by TMG. Then, **4a** is formed via an intramolecular nucleophilic cyclization of **3a**. After that, followed by rearrangement of **4a** through the intermediate isocyanate **5a**, **6a** and the final product **2a** were afforded. Additionally, the formation of the intermediate **5a** assisted by the *o*-cyano group appears to be of great importance in the whole catalytic cycle. In summary, TMG as a catalyst might play a dual role in this reaction: (1) activating the substrate **1a** by deprotonation to facilitate the attack of CO_2; (2) also activating the CO_2 molecule via forming a CO_2–TMG complex.[19] Therefore, the basicity of organic guanidine is considered to be significant for this reaction.



Scheme 3. A plausible mechanism.

3. Conclusions

In conclusion, TMG was developed as an efficient catalyst for the synthesis of several quinazoline-2,4(1*H*, 3*H*)-diones via a chemical fixation of CO_2 to 2-aminobenzonitriles in high isolated yield under solvent-free conditions. Notably, the reaction could work well even at 2 mmol % of catalyst loading or under CO_2 pressure as low as 0.5 MPa. This approach would be more promising from the viewpoint of Green Chemistry and Sustainable Society.

4. Experimental

4.1. Caution

Experiments using compressed CO_2 are potentially hazardous and must only be carried out using the appropriate equipment and under rigorous safety precautions.

4.2. Materials

Guanidines **G1–G3** were synthesized according to the published methods,[21,17a] which were given in Supplementary data. All other guanidines and reagents were obtained commercially without further purification. Carbon dioxide with a purity of 99.99% was commercially available. Toluene and diethyl ether were freshly distilled over sodium under nitrogen. Dichloromethane was distilled from calcium hydride.

4.3. Characterization

^{1}H NMR spectra was recorded at Bruck 300 and 400 or Varian Mercury-Plus 400 spectrometer in $CDCl_3$ or DMSO-d_6 and TMS (0 ppm) was used as internal reference, ^{13}C NMR was recorded at 75 MHz or 100.6 MHz in $CDCl_3$ (or DMSO-d_6) and $CDCl_3$ (77.0 ppm) (or DMSO-d_6, 39.4 ppm) was used as internal reference. High-resolution mass spectrometry was conducted using a Varian 7.0 T FTICR-MS by ESI technique. ESI-MS were recorded on a Thermo Finnigan LCQ Advantage spectrometer in ESI mode with a spray voltage of 4.8 kV. Melting points were measured on an X4 apparatus and uncorrected. Infrared (IR) spectra were recorded on a Bruker Tensor27 FT-IR spectrophotometer with KBr pellets. The characterization data (^{1}H NMR, ^{13}C NMR, IR, and ESI-MS) and physical properties are reported below.

4.4. General procedure for the TMG-catalyzed reaction of CO_2 and 2-aminobenzonitrile

In a typical experiment, to a 50 mL stainless steel autoclave with an inner glass tube were charged with 2-aminobenzonitriles (5 mmol) and guanidine base (0.25 mmol). A certain amount of CO_2 was introduced into the autoclave and then the autoclave was heated to the reaction temperature. Then CO_2 pressure was adjusted to the desired value and the reaction was run under stirring for desired time. After completion of reaction, the autoclave was allowed to be cooled in an ice bath and CO_2 was slowly vented. The residue was treated with 1 N HCl (30 mL), washed with *tert*-butyl methyl ether (20 mL) and dried under vacuum at 60 °C for 4 h to afford the desired product. The products were further identified by NMR and MS (see the Supplementary data), which are consistent with those reported in the literature[13c,16c] and in good agreement with the assigned structures. The NMR charts for the products and guanidines **G1**–**G3** were given in Supplementary data.

4.5. Characterization data

*4.5.1. N-(1,3-Dimethylimidazolidin-2-ylidene) butan-1-amine (**G1**).* Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, ^3J=7.2 Hz, 3H), 1.31–1.40 (m, 2H), 1.47–1.55 (m, 2H), 2.77 (s, 6H), 3.12 (s, 4H), 3.32 (t, ^3J=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.96, 20.32, 35.58, 36.40, 47.20, 49.40, 156.88; ESI-MS calcd for $C_9H_{19}N_3$ 169.27, found 170.39 $(M+H)^+$.

*4.5.2. N-(1,3-Dimethylimidazolidin-2-ylidene) cyclohexanamine (**G2**).* Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15–1.72 (m, 10H), 2.76 (s, 6H), 3.11 (s, 4H), 3.38–3.43 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.2, 25.8, 31.3, 36.5, 44.9, 54.0, 155.4; ESI-MS calcd for $C_{11}H_{21}N_3$ 195.30, found 196.26 $(M+H)^+$; HRMS: calcd for $C_{11}H_{21}N_3$ $(M+H)^+$ 196.1808, found 196.1804.

*4.5.3. 2-Butyl-1,1,3,3-tetramethylguanidine (**G3**).* Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, ^3J=7.4 Hz, 3H), 1.28–1.37 (m, 2H), 1.46–1.53 (m, 2H), 2.64 (s, 6H), 2.73 (s, 6H), 3.09 (t, ^3J=7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.3, 34.6, 38.6, 39.0, 39.4, 48.8, 159.7; ESI-MS calcd for $C_9H_{21}N_3$ 171.28, found 172.27 $(M+H)^+$.

4.6. Quinazoline-2,4(1*H*, 3*H*)-dione (2a)

White solid. Mp>300 °C (lit.[16c] >300 °C). IR (KBr) 3253, 3054, 2846, 1702, 1670, 1618, 1443, 755 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.14–7.19 (m, 2H), 7.63 (t, ^3J=7.7 Hz, 1H), 7.88 (d, ^3J=7.7 Hz, 1H), 11.13 (s, 1H), 11.27 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 114.2, 115.2, 122.2, 126.9, 134.8, 140.8, 150.2, 162.7; ESI-MS calcd for $C_8H_6N_2O_2$ 162.15, found 161.17$(M-H)^-$.

*4.6.1. 6,7-Dimethoxyquinazoline-2,4(1H, 3H)-dione (**2b**).* Light yellow solid. Mp>300 °C (lit.[16c] >300 °C). IR (KBr) 3471, 3379, 3294, 1708, 1653, 1625, 1467, 1436, 1265, 1099 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.74 (s, 3H), 3.78 (s, 3H), 6.63 (s, 1H), 7.22 (s, 1H), 10.90 (s, 1H), 11.08 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 55.6, 55.7, 97.6, 106.1, 107.3, 136.4, 144.9, 150.3, 154.8, 162.3; ESI-MS calcd for $C_{10}H_{10}N_2O_4$ 222.2, found 221.07$(M-H)^-$.

*4.6.2. 7-Chloroquinazoline-2, 4(1H,3H)-dione (**2c**).* Light yellow solid. Mp>300 °C (lit.[16c] >300 °C). IR (KBr) 3305, 3047, 1743, 1683, 1617, 1430, 1284, 862 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 (s, 1H), 7.20 (d, ^3J=8.4 Hz, 1H), 7.86 (d, ^3J=7.2 Hz, 1H), 11.25 (s, 1H), 11.41 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 113.2, 114.5, 122.3, 128.9, 139.2, 141.8, 150.0, 162.0; ESI-MS calcd for $C_8H_5ClN_2O_2$ 196.59, found 195.21$(M-H)^-$.

*4.6.3. 6-Chloroquinazoline-2, 4(1H,3H)-dione (**2d**).* White solid. Mp>300 °C (lit.[16c] >300 °C). IR (KBr) 3198, 3058, 1711, 1668, 1483, 1428, 1284, 877 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.17 (d, ^3J=8.8 Hz, 1H), 7.68 (d, ^3J=8.8 Hz, 1H), 7.81 (s, 1H), 11.32 (s, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 115.7, 117.5, 125.8, 126.1, 134.6, 139.7, 150.0, 161.7; ESIMS calcd for $C_8H_5ClN_2O_2$ 196.59, found 195.17 $(M-H)^-$.

*4.6.4. 6-Bromoquinazoline-2,4(1H,3H)-dione (**2e**).* White solid. Mp>300 °C (lit.[13c] >300 °C). IR (KBr) 3193, 3066, 1742, 1701, 1613, 1480, 1433, 1286, 836 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, ^3J=8.7 Hz, 1H), 7.78 (dd, ^2J=8.8 Hz, ^3J=2.3 Hz, 1H), 7.93 (d, ^3J=2.3 Hz, 1H), 11.26 (s, 1H), 11.43 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 113.7, 116.1, 117.6, 128.8, 137.4, 139.9, 149.9, 161.6; HRMS: calcd for $C_8H_5BrN_2O_2$ $(M-H)^-$ 238.9462, found 238.9455.

*4.6.5. 6-Fluoroquinazoline-2,4(1H,3H)-dione (**2f**).* White solid. Mp>300 °C. IR (KBr) 3199, 3059, 1714, 1675, 1635, 1500, 1439, 1288, 884 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (q, ^4J=8.8 Hz, 1H), 7.52–7.60 (m, 2H), 11.20 (s, 1H), 11.41 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ (111.7, 112.0), (115.2, 115.3), (117.4, 117.5), (122.7, 122.9), 137.4, 150.0, (156.0, 158.4), (162.05, 162.07); HRMS calcd for $C_8H_5FN_2O_2$ $(M-H)^-$ 179.0262, found 179.0255.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.04.011. These data include MOL files and InChIKeys of the most important compounds described in this article.

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