ChemPubSoc Europe

DOI: 10.1002/chem.201500573

CHEMISTRY A European Journal Full Paper

Cyclic Oxoguanidines

Synthesis and Mechanistic Study of Cyclic Oxoguanidines via $Zn(OTf)_2$-Catalyzed Guanylation/Amidation from Readily Available Amino Acid Esters and Carbodiimides

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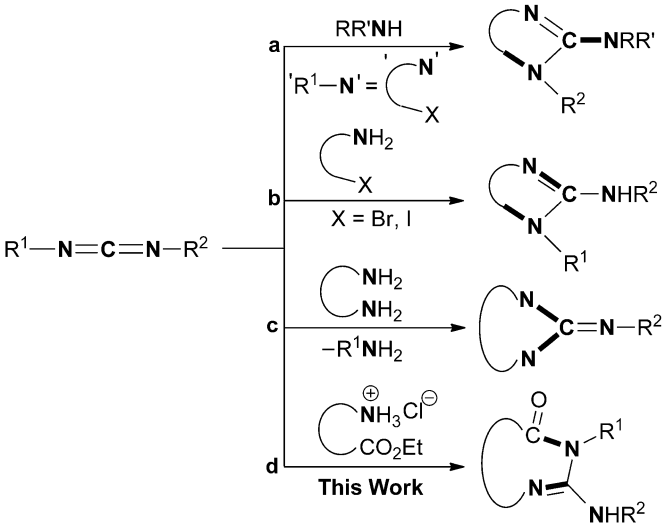
Abstract: The $Zn(OTf)_2$-catalyzed guanylation/amidation from readily available amino acid esters and carbodiimides is achieved to provide efficiently various cyclic oxoguanidines, including 2-amino-1*H*-imidazol-5(4*H*)-ones and 2-aminoquinazolin-4(3*H*)-ones in medium-to-high yields. It is the first time that an ammonium salt has been used in a guanylation reaction. The application of cyclic oxoguanidines to provide the conjugated heterocyclic compounds via oxidative C–N formation or aldol reaction is explored. The reaction mechanism is well elucidated by the isolation and characterization of three important intermediates.

Introduction

Recent years have witnessed a rapid growth in the area of the catalytic guanylation reaction of amines with carbodiimides (CGAC reaction).[1] This is because CGAC reaction provides a straightforward and atom-economical method to prepare substituted guanidines (RN=C(NR′R′′)NHR), which have unique value in pharmaceutical chemistry,[2] organometallic and coordination chemistry,[3] and organic synthesis.[4] Very recently, tandem guanylation/cyclization reaction became a hot field because of the fast and efficient construction of N-containing heterocycles through the transformation of N–H, C–N, and C=N bonds of guanidines.[1a,5–7] Three important strategies in these two-component CGAC reactions have been applied to the synthesis of cyclic guanidines: 1) Cu-catalyzed guanylation/*N*-arylation cyclization of amines with *o*-haloarylcarbodiimides (Scheme 1 a);[5] 2) Cu-catalyzed guanylation/*N*-arylation cyclization of *o*-haloanilines with carbodiimides (Scheme 1 b);[6] and 3) Ti-catalyzed guanylation/metathesis cyclization of diamines with carbodiimides (Scheme 1 c).[7] Our group is interested in the synthesis of guanidines by using the CGAC reaction,[8,9] and the reactivity research of carbodiimides.[10] Herein we report a tandem $Zn(OTf)_2$-catalyzed guanylation/amidation process from readily available amino acid ester hydrochlorides and carbodiimides to efficiently construct five-membered cyclic oxoguanidines (Scheme 1 d). It is the first time to use the ammonium salt in guanylation reaction, and this type of heterocyclic compound was reported to show good bioactivity[11] or could be used as ligands.[12] In addition, an ethyl 2-aminobenzoate can also act as a suitable partner to efficiently construct six-membered cyclic oxoguanidines.



Scheme 1. Models of two-component guanylation/cyclization for the synthesis of cyclic guanidines.

Results and Discussion

Synthesis of cyclic oxoguanidines

Condition screening for cyclic oxoguanidines

The reaction of glycine ethyl ester hydrochloride (**1 a**) with *N*,*N*′-diisopropylcarbodiimide (*i*PrN=C=N*i*Pr, DIC) was first examined under various conditions. As a control experiment, DIC

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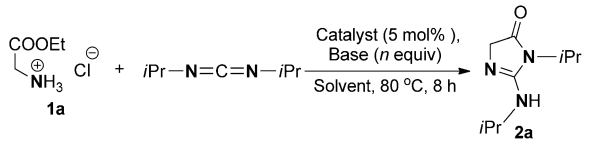
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500573.

Table 1. Optimization of the reaction conditions.



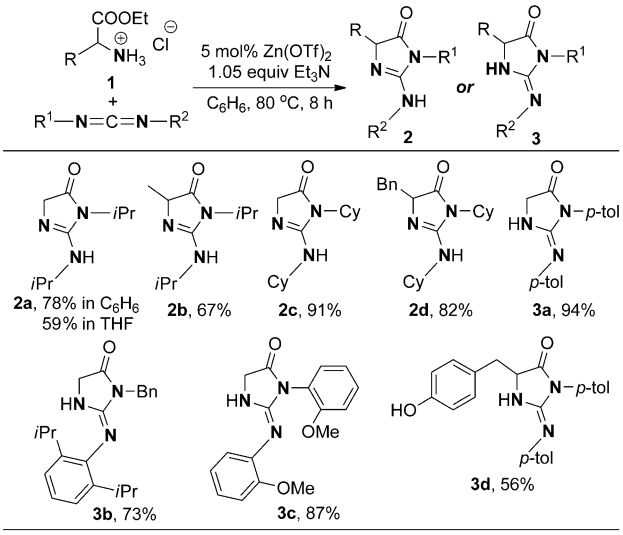
Entry	Catalyst	Base (equiv)	Solvent	**2a** yield [%][a]
1	none	none	C_6H_6	0
2	none	Et_3N (1.05)	C_6H_6	6
3	none	Et_3N (2)	C_6H_6	8
4	$Zn(OTf)_2$	none	C_6H_6	0
5	$Zn(OTf)_2$	Et_3N (1.05)	C_6H_6	78[b]
6	$Zn(OTf)_2$	Et_3N (1.05)	THF	59
7	$Zn(OTf)_2$	Et_3N (1.05)	toluene	56
8	$ZnCl_2$	Et_3N (1.05)	C_6H_6	41
9	$CoCl_2$	Et_3N (1.05)	C_6H_6	0
10	$PdCl_2$	Et_3N (1.05)	C_6H_6	60
11	CuCl	Et_3N (1.05)	C_6H_6	29
12	$CuCl_2$	Et_3N (1.05)	C_6H_6	0

[a] GC yield. [b] Isolated yield.

was heated with **1a** in benzene at 80 °C, but no reaction was observed in 8 h (Table 1, entry 1). When 1–2 equiv of Et_3N were added, only a small amount of cyclic oxoguanidine (**2a**) was obtained (Table 1, entries 2 and 3). Because this reaction needed a long time and gave a low yield without catalyst,[13] we tried various metal salts, such as $Zn(OTf)_2$, CuCl, $CuCl_2$, $CoCl_2$ and $PdCl_2$ in this system (Table 1, entries 4–12). The amino acid ester hydrochloride salt has poor solubility in common solvents, such as THF, benzene and toluene. However, Et_3N is required in this methodology to neutralize hydrochloric acid to liberate the free amino acid ester, which has the better solubility in common solvents (Table 1, entry 4). These reaction conditions show the present reaction is not a simple proton-promoted reaction. Finally, we found that **2a** could be obtained in 78% isolated yield by using $Zn(OTf)_2$ (5 mol%) as a catalyst and benzene as solvent at 80 °C for 8 h (Table 1, entry 5). THF could be the alternative solvent instead of benzene (Table 1, entry 6).

Synthesis of cyclic oxoguanidines including 2-aminoimidazolones (2) or 2-iminoimidazolidin-4-ones (3)

As summarized in Scheme 2, this method could be applied in different amino acid ester hydrochlorides, such as **1a**, alanine ethyl ester hydrochloride (**1b**) and phenylalanine ethyl ester hydrochloride (**1c**). Different carbodiimides (*i*PrN=C=N*i*Pr, CyN=C=NCy, TolN=C=NTol, and DippN=C=NBn) could also be utilized to provide cyclic oxoguanidines **2a–d** or **3a–d** in medium to high yields. When R^1 and R^2 in the carbodiimides are alkyl groups, 2-aminoimidazolones **2a–d**, in which the C=N double bond is within the five-membered ring, were exclusively observed. The solid-state structure of **2c** has been confirmed by previous work.[14] In contrast, when R^2 in the carbodiimides are aryl groups, 2-iminoimidazolidin-4-ones **3a–d** were exclusively obtained as an isomer of 2-aminoimidazolones. The



Scheme 2. Synthesis of cyclic oxoguanidines **2a–d** and **3a–d**.

reason may be the conjugated effect between C=N double bond and aryl substituent. It should be noted that OMe and OH group are tolerated (**3c**,**d**). When an unsymmetric carbodiimide (DippN=C=NBn) was utilized, the regioselective isomer **3b** was produced, probably due to the steric hindrance of the Dipp group. Single-crystal X-ray diffraction analysis of **3b** shows that the nitrogen atom adjoining the less steric Bn group connects with the C=O group, and the C=N double bond is outside of the five-membered ring (Figure 1).

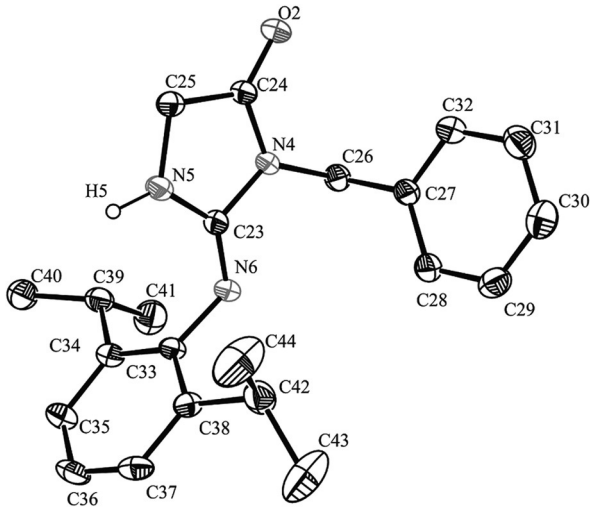
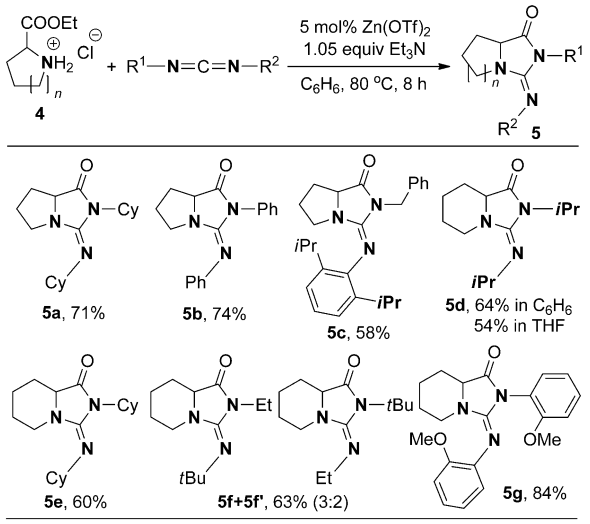


Figure 1. ORTEP drawing of **3b** with 30% thermal ellipsoids. Hydrogen atoms, except that of the nitrogen atom N5, are omitted for clarity.

When cyclic amino acid ester hydrochlorides **4** were applied to the present conditions, the bicyclic-fused 2-iminoimidazolidin-4-ones **5a–g** could be synthesized (Scheme 3). Similar to the regioselectivity of **3b** in Scheme 2, **5c** could be exclusively obtained when the unsymmetric carbodiimide DippN=C=NBn was utilized. In case of *t*BuN=C=NEt, the products were a pair of isomers **5f** and **5f′**.

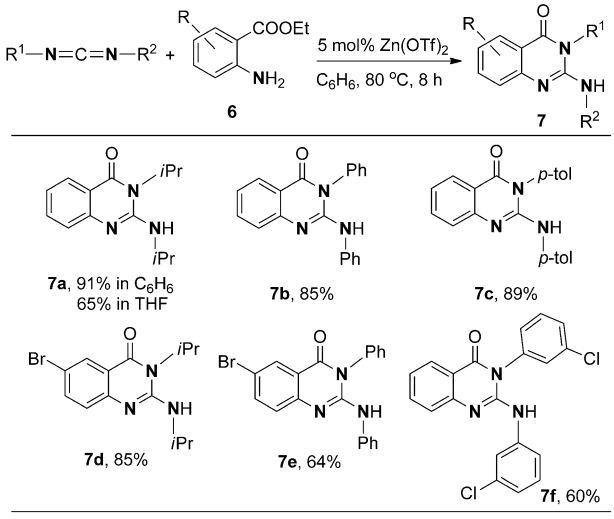


Scheme 3. Synthesis of bicycle-fused 2-iminoimidazolidin-4-ones **5a–g**.

There are some previous reports on the synthesis of 2-iminoimidazolidin-4-ones.[15] However, they usually need ester-substituted carbodiimides as starting materials, which are not commercially available, and difficult to prepare. What is more, these methods could not be applied in the synthesis of bicyclic-fused 2-iminoimidazolidin-4-ones like **5** in Scheme 3. The present method provides a convenient way to build these cyclic oxoguanidines **5**.

Synthesis of 2-aminoquinazolinones

The above guanylation/amidation process of amino acid ester hydrochlorides **1** or **4** with carbodiimides provided various five-membered cyclic oxoguanidines. Similarly, changing **1** to ethyl 2-aminobenzoates **6**, a series of six-membered cyclic oxoguanidines **7a–e** could be obtained. These results were summarized in Scheme 4. Various carbodiimides could be applied



Scheme 4. Synthesis of 2-aminoquinazolinones **7a–f**.

in this method and the yields are high (**7a–c**). Halogen atoms were also be tolerated under these conditions (**7d–f**). The structure of **7c** was confirmed by X-ray crystallographic analysis (Figure 2). It clearly shows the core structure of 2-aminoquinazolinone with the inner C=N bond in the six-membered ring.

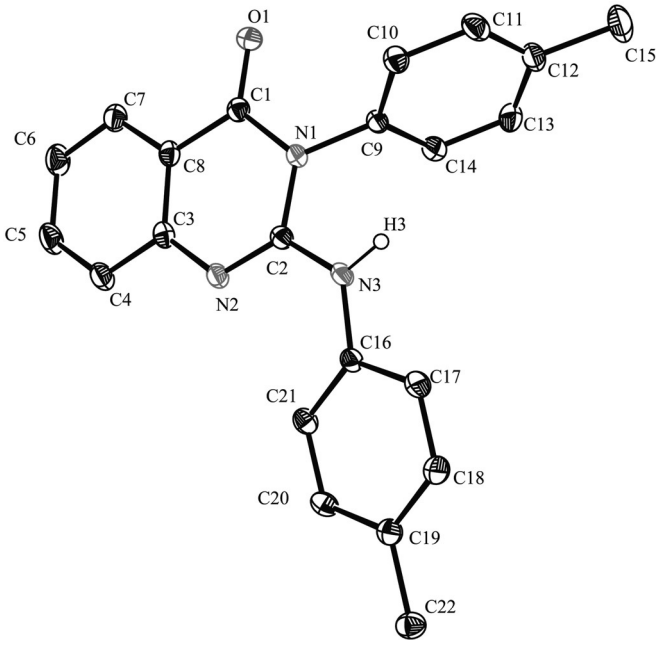


Figure 2. ORTEP drawing of **7c** with 30% thermal ellipsoids. Hydrogen atoms, except that of the nitrogen atom N3, are omitted for clarity.

Application of cyclic oxoguanidines

Further transformation of these products was explored. Because there is a free N–H bond in these cyclic oxoguanidines, it could easily be applied in oxidative C–N bond formation. When **3a** or **7b** were treated with one equivalent of $PhI(OAc)_2$, the ring-closed products **8** or **9** could be obtained in 84 and 60%, respectively [Eqs. (1) and (2)].[16] Single-crystal X-ray diffraction analysis of **8** reveals it is a highly conjugated molecule with nearly all the atoms in one plane (Figure 3). This method provides a new route for the synthesis of conjugated heterocyclic compounds by mean of a two-step procedure from easily

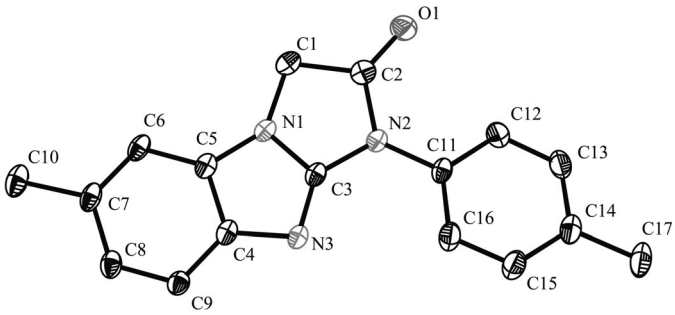
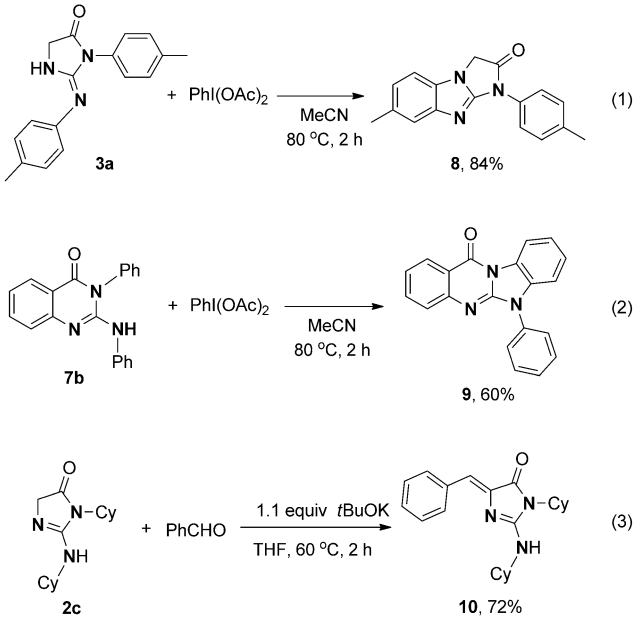


Figure 3. ORTEP drawing of **8** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

available reagents. These compounds were reported to have potential value in material science.[17]

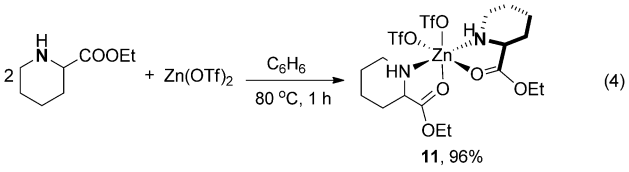
Compound **2c** could be also applied in an aldol reaction to prepare **10** [Eq. (3)], which is similar to Leucettamine, isolated from marine sponges. Such structures have drawn much attention based on their bioactivity.[18]



Mechanistic study

Isolation and reaction of three important intermediates

Catalytic guanylation reaction of amines with carbodiimides (CGAC reaction) is an atom-economical reaction for the preparation of guanidines. From experimental evidence to theoretical chemistry,[19] the mechanistic study has received much attention. Different types of reaction mechanisms have been reported.[1] To gain information on the reaction mechanism, the stoichiometric reaction was carried out to isolate and characterize some important intermediates. When ethyl 2-piperidinecarboxylate was mixed with one equivalent of $Zn(OTf)_2$ and stirred in benzene at 80 °C for 1 h, a Zn complex **11** was obtained in 96% yield [Eq. (4)]. This structure was confirmed by X-ray crystallographic analysis (Figure 4). It adopts a monomer structure that is totally different to the intermediate of other Zn-catalyzed guanylation reactions.[8e] The zinc center is encapsulated in an octahedral ligand field with C_2 symmetry in the solid state. Two amino acid esters coordinate to the zinc center as chelating ligands in a five-membered ring, while another two OTf groups coordinate to it at the *ortho*-position. Interestingly, the length between H1 and O5′ (2.012 Å), and the bond angle of N1′-H1′-O5 (159.9°) clearly show the OTf groups from hydrogen-bonding interactions with the NH groups in the six-membered rings. These hydrogen bonds may weaken the N–H bond and promote the protonation process during the reaction.



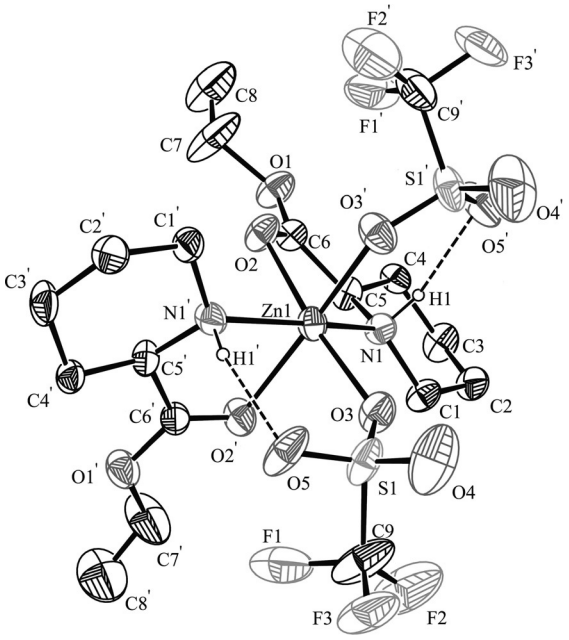
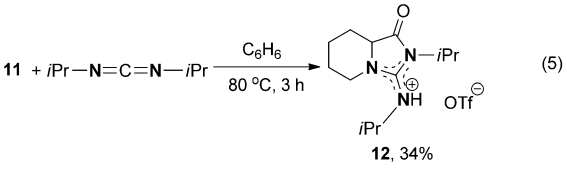


Figure 4. ORTEP drawing of **11** with 30% thermal ellipsoids. Hydrogen atoms, except those on nitrogen atoms, are omitted for clarity. The trifluoromethyl part of **11** is disordered. The major part is shown above. Selected bond lengths [Å]: Zn1–N1 2.045(5), Zn1–O2 2.219(5), Zn1–O3 2.120(0), C6–O1 1.301(8), C6–O2 1.195(7), S1–O3 1.428(5), S1–O4 1.425(8), S1–O5 1.393(5). Hydrogen bonds: $d_{H1'\cdots O5}=2.102$ Å, $d_{N1'\cdots O5}=2.973$ Å, $\measuredangle$N1′–H1′···O5 = 159.9°; $d_{H1\cdots O5'}=2.102$ Å, $d_{N1\cdots O5'}=2.973$ Å, $\measuredangle$N1–H1··O5′ = 159.9°.

When compound **11** was allowed to react with carbodiimide [Eq. (5)], a guanidinium trifluoromethanesulfonate salt **12** was isolated. The structure of **12** was confirmed by X-ray crystallographic analysis (Figure 5). Compound **12** has one crystallographically independent cation–anion pair in the asymmetric unit. The sum of the angles at central carbon equals 360° indicating complete planarity within the range of errors. The C–N bond lengths are in the range of 1.32–1.38 Å within the "CN_3" core suggesting the delocalization within the π-system of the "CN_3" core of the guanidinium cation.



When **11** was allowed to react with carbodiimide at 40 °C, an open guanidine intermediate **13** could be isolated in 29% yield with the concomitant formation of the final ring-closed

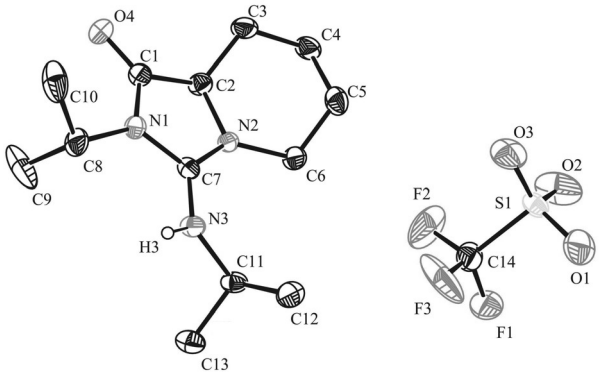
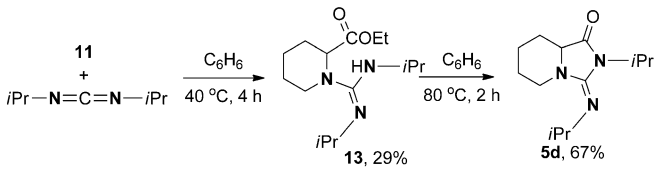


Figure 5. ORTEP drawing of **12** with 30% thermal ellipsoids. Hydrogen atoms, except that on nitrogen atom N3, are omitted for clarity. Selected bond lengths [Å] and angles [°]: N1–C7 1.383 (4), N2–C7 1.325(4), N3–C7 1.309(4), N1-C7-N2 110.2(3), N1-C7-N3 121.3(3), N2-C7-N3 128.4(3).

product **5d**. Increasing the temperature, **13** could be transformed to **5d** (Scheme 5). It clearly shows that the guanylation/amidation reaction proceeds via the open guanidine intermediate.

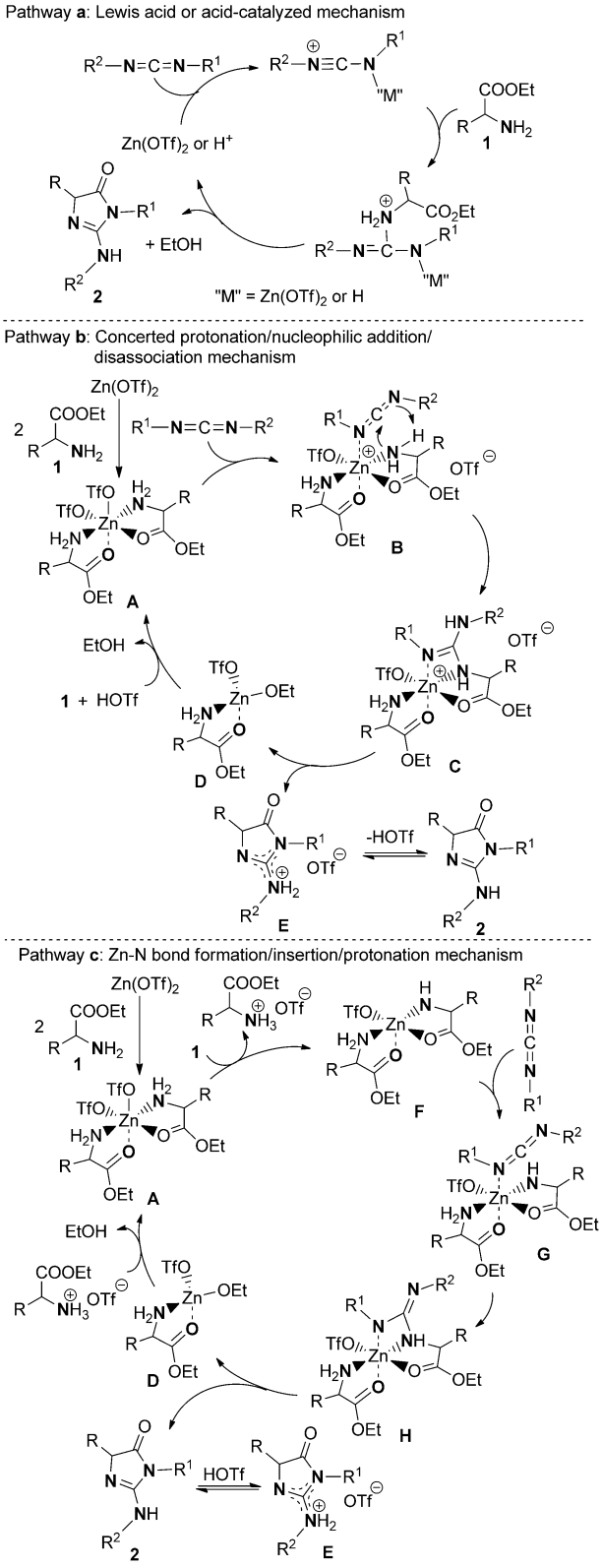


Scheme 5. Isolation and reaction of the opening guanidine intermediate **13**.

Three possible mechanisms

Generally, $Zn(OTf)_2$ is regarded as a Lewis acid. Therefore, it is possible for $Zn(OTf)_2$ to act as a Lewis acid to activate the carbodiimide. Followed by nucleophilic addition/intramolecular proton transfer, the catalytic cycle is completed by releasing guanidines and regenerating $Zn(OTf)_2$ as shown in pathway **a** in Scheme 6. Similarly, a proton acid-catalyzed mechanism is also proposed. However, this mechanism could not explain the formation of trifluoromethanesulfonate salt **12**. In addition, some other Lewis acids show lower catalytic activity than $Zn(OTf)_2$ (Table 1). Therefore, we think it is not a simple Lewis acid catalyzed reaction, and pathway **a** could be excluded.

The formation of **12** reveals $Zn(OTf)_2$ should go through a ligand exchange step in this reaction. Based on the isolation and features of two important intermediates **11** and **12**, we proposed two other possible mechanisms: 1) Concerted protonation/nucleophilic addition/disassociation mechanism (Scheme 6, pathway **b**). Ligand substitution by the coordination of the carbodiimide and the disassociation of OTf anion would yield the zinc salt intermediate **B**. After nucleophilic addition step/protonation, **B** might change to intermediate **C**. Followed by the amidation step, **C** could release **E** and intermediate **D**, which could in turn react with another molecule of



Scheme 6. Three possible mechanisms for the formation of **2**.

1 to finish the catalytic cycle. 2) Zn–N bond formation/insertion/protonation mechanism (Scheme 6, pathway **c**). The elimination of HOTf followed by neutralization would generate intermediate **F**, which contains the active Zn–N bond and in-

creases the nucleophilicity on the N atom. Coordination of carbodiimide to **F**/intramolecular insertion might provide intermediate **H**. Intramolecular nucleophilic amidation in **H** should release **2** and yield intermediate **D**. The interaction between **D** with amino acid ester hydrotrifluoromethanesulfonate would regenerate **A** to complete the catalytic cycle.

Coordination of the nitrogen atom of amino acid ester to zinc in **A** would decrease the nucleophilicity of amine compared to the free uncoordinated amine.[9c] The coordination of carbodiimide to zinc might overcompensate this negative effect of zinc coordination to amine in **B** (Scheme 6, pathway **b**). Therefore, the nucleophilic addition/protonation step from **B** to **C** should be a rate-determining step. The hydrogen bonds in **11** show the interaction between H atom on the N atom of piperidine ring and O atom of OTf group (Figure 4). The interaction of hydrogen bonds could weaken the strength of the N–H bond, and promote the elimination of HOTf yielding the active Zn–N bond (Scheme 6, pathway **c**). The formation of Zn–N bond is useful for the nucleophilic addition into carbodiimides. This also explains why $ZnCl_2$ has the lower catalytic activity (Table 1, entry 6) because the Cl atom is difficult to form the hydrogen bond like Zn complex **11**. For these reasons, we consider that pathway **c** might be more reasonable than pathway **b**.

Conclusion

We have developed an efficient method to synthesize a series of cyclic oxoguanidines, including 2-amino-1*H*-imidazol-5(4*H*)-ones and 2-aminoquinazolin-4(3*H*)-ones in medium to high yields by means of $Zn(OTf)_2$-catalyzed guanylaion/amidation. These cyclic oxoguanidines could have the potential bioactivities or could be used as ligands. All the starting materials, including carbodiimides, amino acid esters, and $Zn(OTf)_2$, are cheap and commercially available. It is the first time that ammonium salts have been applied in a guanylation reaction. Further application of cyclic oxoguanidines was carried out to provide the conjugated heterocyclic compounds. In addition, three important intermediates were isolated and characterized from the reaction system. These are very useful in helping us to understand the catalytic mechanism.

Experimental Section

General methods

Unless otherwise noted, all starting materials were commercially available and were used without further purification. Solvents were purified by an Mbraun SPS-800 Solvent Purification System and dried over fresh Na chips in the glovebox. All reactions were carried out under air atmosphere. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX400 spectrometer (FT, 400 MHz for ^1H; 100 MHz for ^{13}C) at room temperature, unless otherwise noted. High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI (electrospray ionization).

Typical procedure for the preparation of 2-aminoimidazolones 2a–d or 2-iminoimidazolidin-4-ones 3a–d by the reaction of amino acid ester hydrochloride and carbodiimide

In a 25 mL of flask, triethylamine (1.05 mmol, 106 mg) was added to an amino acid ester hydrochloride (1.05 mmol) in benzene (5 mL). Then $Zn(OTf)_2$ (0.05 mmol, 18 mg) and carbodiimide (1.00 mmol) were added to the flask, and the mixture was stirred at 80 °C for 8 h. The solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give products **2a–d** or **3a–d**.

Data for 2a: Yellow oil, isolated yield 78% (143 mg); ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.24$ (d, $J = 6.5$ Hz, 6H; CH_3), 1.42, (d, $J = 7.0$ Hz, 6H; CH_3), 3.92–3.94 (m, 3H; $1CH_2$, 1CH), 4.15–4.22 (m, 1H; CH), 4.79 ppm (brs, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 20.06$, 22.75, 43.46, 43.57, 56.19, 155.55, 180.31 ppm; IR (film): $\tilde{\nu} = 3387$ (N–H), 1676 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_9H_{18}N_3O$ $[M+H]^+$: 184.1449; found: 184.1439.

Data for 2b: Yellow oil, isolated yield 67% (132 mg); ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.12$ (d, $J = 6.4$ Hz, 3H; CH_3), 1.23 (brs, 3H; CH_3), 1.34, (d, $J = 7.2$ Hz, 3H; CH_3), 1.40–1.43 (m, 6H; CH_3), 3.86–3.94 (m, 2H; CH), 4.19 (brs, 1H; CH), 5.00–5.01 ppm (m, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 17.95$, 19.74, 22.93, 23.09, 23.30, 41.44, 43.49, 157.26, 174.82 ppm; IR (film): $\tilde{\nu} = 3282$ (N–H), 1672 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{10}H_{20}N_3O$ $[M+H]^+$: 198.1606; found: 198.1596.

Data for 2c: Yellow solid, isolated yield 91% (239 mg); m.p. 86.6–87.6 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.17$–1.42 (m, 8H; CH_2), 1.62–1.75 (m, 6H; CH_2), 1.85–2.05 (m, 6H; CH_2), 3.69 (brs, 1H; CH), 3.95 (s, 2H; CH_2), 4.10 ppm (brs, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 24.72$, 25.05, 25.56, 25.93, 30.25, 33.31, 50.33, 52.05, 56.19, 155.64, 180.28 ppm; IR (film): $\tilde{\nu} = 3326$ (N–H), 1620 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{15}H_{26}N_3O$ $[M+H]^+$: 264.2076; found: 264.2067. The single-crystal structure **2c** was consistent with that reported.[14]

Data for 2d: Yellow solid, isolated yield 82% (290 mg); m.p. 96.7–97.6 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.13$–1.27 (m, 7H; CH_2), 1.34–1.43 (m, 3H; CH_2), 1.61–1.71 (m, 8H; CH_2), 1.92–2.02 (m, 2H; CH_2), 3.14 (d, $J = 6.4$ Hz, 2H; CH_2), 3.36 (brs, 1H; CH), 3.73 (brs, 2H; CH), 4.20 (brs, 1H; NH), 7.10–7.18 ppm (m, 5H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 14.00$, 24.40, 24.59, 24.97, 25.51, 25.76, 29.64, 33.06, 33.83, 37.79, 40.98, 51.54, 55.67, 60.73, 126.76, 127.57, 128.50, 129.28, 130.19, 136.12, 137.26, 175.00 ppm; IR (film): $\tilde{\nu} =$ 3378 (N–H), 1680 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{22}H_{32}N_3O$ $[M+H]^+$: 354.2545; found: 354.2544.

Data for 3a: Yellow solid, isolated yield 94% (262 mg); m.p. 147.6–148.5 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 2.33$ (s, 3H; CH_3), 2.42 (brs, 3H; CH_3), 3.94 (brs, 1H; CH_2), 4.26 (brs, 1H; CH_2), 4.92 (brs, 1H; NH), 6.85–6.87 (m, 1H; CH), 7.12 (d, $J = 7.9$ Hz,, 2H; CH), 7.33 ppm (brs, 5H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 20.73$, 21.16, 46.95, 119.45, 122.02, 127.07, 129.71, 130.98, 132.45, 138.27, 144.78, 150.73, 170.66 ppm; IR (film): $\tilde{\nu} = 3325$ (N–H), 1687 (C=O); HRMS: *m/z* calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$: 280.1450; found: 280.1442.

Data for 3b: Yellow solid, isolated yield 73% (255 mg); m.p. 166.5–167.5 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.08$–1.10 (m, 12H; CH_3), 2.82–2.89 (m, 2H; CH), 3.86 (s, 2H; CH_2), 4.25 (brs, 1H; NH), 4.91 (s, 2H; CH_2), 7.00–7.10 (m, 3H; CH), 7.26–7.34 (m, 3H; CH), 7.50–7.52 ppm (m, 2H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta =$ 23.39, 23.42, 28.08, 42.61, 46.90, 123.20, 123.51, 127.59, 128.34, 128.63, 136.48, 139.81, 142.02, 147.92, 170.98 ppm; IR (film): $\tilde{\nu} =$ 3282 (N–H), 1671 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{22}H_{28}N_3O$ $[M+$

H]$^+$: 350.2232; found: 350.2226. Single crystals of **3b** suitable for X-ray analysis were grown in ethyl acetate/hexane at room temperature for three days.

Data for 3c: Yellow solid, isolated yield 87% (262 mg); m.p. 156.5–157.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.68 (s, 3H; CH_3), 3.81 (s, 3H; CH_3), 4.33 (brs, 2H; CH_2), 6.78–7.80 (m, 1H; CH), 6.94–6.96 (m, 2H; CH), 7.06–7.10 (m, 2H; CH), 7.28–7.29 (m, 1H; CH), 7.46 (brs, 1H; CH), 8.33 ppm (brs, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 55.80, 55.84, 57.39, 109.96, 112.46, 118.57, 120.02, 121.20, 121.41, 122.52, 128.12, 130.07, 131.41, 147.65, 152.35, 155.31, 178.85 ppm; IR (film): $\tilde{\nu}$ = 3336 (N–H), 1655 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{18}H_{22}N_3O_3$ [*M*+H]$^+$: 328.1661; found: 328.1656.

Data for 3d: Colorless solid, isolated yield 56% (216 mg); m.p. 176.8–178.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.28 (s, 6H; CH_3), 2.98–3.09 (m, 2H; CH_2), 4.30 (brs, 1H; CH), 4.79 (brs, 1H; NH), 6.63 (d, *J* = 8.0 Hz, 2H; CH), 6.74 (d, *J* = 7.7 Hz, 2H; CH), 6.98 (d, *J* = 7.9 Hz, 2H; CH), 7.07–7.09 (m, 4H; CH), 7.16 ppm (d, *J* = 7.9 Hz, 2H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 20.80, 21.18, 37.41, 58.58, 115.54, 122.12, 125.80, 127.18, 129.12, 129.75, 129.84, 129.97, 130.75, 132.73, 132.79, 138.55, 144.45, 150.36, 155.68, 172.60 ppm; IR (film): $\tilde{\nu}$ = 3317 (N–H), 1660 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{24}H_{24}N_3O_2$ [*M*+H]$^+$: 386.1868; found: 386.1876.

Typical procedure for the preparation of bicycle-fused 2-iminoimidazolidin-4-ones 5a–g by the reaction of amino acid ester hydrochloride and carbodiimide

In a 25 mL of flask, triethylamine (1.05 mmol, 106 mg) was added to an amino acid ester hydrochloride (1.05 mmol) in benzene (5 mL). Then $Zn(OTf)_2$ (0.05 mmol, 18 mg) and carbodiimide (1.00 mmol) were added to the flask, and the mixture was stirred at 80 °C for 8 h. The solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give products **5a–g**.

Data for 5a: Colorless solid, isolated yield 71% (215 mg); m.p. 28.7–29.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.25–1.34 (m, 6H; CH_2), 1.41–1.49 (m, 1H; CH_2), 1.54–1.63 (m, 5H; CH_2), 1.67–1.79 (m, 6H; CH_2), 1.91–1.97 (m, 2H; CH_2), 2.17–2.35 (m, 4H; CH_2), 3.10–3.17 (m, 1H; CH), 3.43–3.52 (m, 2H; CH_2), 3.90 (t, *J* = 7.9 Hz, 1H; CH), 3.97–4.03 ppm (m, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 24.34, 24.73, 25.12, 25.75, 25.77, 25.85, 26.76, 28.25, 28.28, 30.66, 34.65, 35.74, 51.79, 52.18, 55.69, 64.28, 151.04, 173.97 ppm; IR (film): $\tilde{\nu}$ = 1670 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{18}H_{30}N_3O$ [*M*+H]$^+$: 304.2389; found: 304.2379.

Data for 5b: Colorless solid, isolated yield 74% (215 mg); m.p. 88.9–89.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.24–1.27 (m, 1H; CH_2), 1.84–1.98 (m, 2H; CH_2), 2.29–2.30 (m, 1H; CH_2), 2.94 (brs, 2H; CH_2), 4.26 (t, *J* = 8.0 Hz, 1H; CH), 6.93–7.01 (m, 3H; CH), 7.22–7.26 (m, 2H; CH), 7.32–7.34 (m, 1H; CH), 7.46 ppm (brs, 4H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 27.23, 28.63, 50.20, 64.76, 122.17, 122.34, 127.14, 128.00, 128.70, 128.84, 132.87, 147.81, 152.39, 172.77 ppm; IR (film): $\tilde{\nu}$ = 1689 (C=O); HRMS: *m/z* calcd for $C_{18}H_{18}N_3O$ [*M*+H]$^+$: 292.1450; found: 292.1440.

Data for 5c: Colorless solid, isolated yield 58% (226 mg); m.p. 125.9–126.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 0.97 (d, *J* = 6.8 Hz, 3H; CH_3), 1.06–1.12 (m, 6H; CH_3), 1.19 (d, *J* = 6.8 Hz, 3H; CH_3), 1.72–1.74 (m, 2H; CH_2), 2.12–2.14 (m, 2H; CH_2), 2.50 (brs, 1H; CH), 2.82–2.86 (m, 2H; CH_2), 2.95–3.00 (m, 1H; CH), 4.06–4.08 (m, 1H; CH), 4.77–4.91 (m, 2H; CH_2), 6.98–7.07 (m, 3H; CH), 7.25–7.36 (m, 3H; CH), 7.44–7.45 ppm (m, 2H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 22.11, 22.78, 23.60, 24.48, 27.25, 28.06, 28.21, 28.81, 43.15, 47.77, 64.76, 122.36, 122.89, 123.28, 127.50, 128.42, 128.56, 136.96, 137.91, 139.82, 142.60, 148.17, 173.42 ppm; IR (film): $\tilde{\nu}$ = 1672 cm^{-1} (C=O); HRMS: m/z calcd for $C_{25}H_{32}N_3O$ [*M*+H]$^+$: 390.2545; found: 390.2546.

Data for 5d: Colorless solid, isolated yield 64% (152 mg); m.p. 49.9–50.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.12–1.15 (m, 6H; CH_3), 1.28–1.29 (m, 1H; CH_2), 1.35–1.38 (m, 6H; CH_3), 1.45–1.52 (m, 2H; CH_2), 1.65–1.68 (m, 1H; CH_2), 1.93–1.96 (m, 1H; CH_2), 2.07–2.10 (m, 1H; CH_2), 3.04–3.10 (m, 1H; CH_2), 3.47–3.50 (m, 1H; CH_2), 3.99–4.02 (m, 1H; CH), 4.15–4.18 (m, 1H; CH), 4.45–4.49 ppm (m, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 19.04, 19.14, 22.96, 25.57, 25.62, 25.82, 27.83, 43.37, 44.44, 45.02, 59.33, 141.13, 172.63 ppm; IR (film): $\tilde{\nu}$ = 1668 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{13}H_{24}N_3O$ [*M*+H]$^+$: 238.1919; found: 238.1913.

Data for 5e: Colorless solid, isolated yield 60% (191 mg); m.p. 36.0–36.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.23–1.39 (m, 10H; CH_2), 1.57–1.59 (m, 6H; CH_2), 1.72–1.78 (m, 6H; CH_2), 1.92–1.95 (m, 1H; CH_2), 2.06–2.10 (m, 1H; CH_2), 2.21–2.33 (m, 2H; CH_2), 3.02–3.08 (m, 1H; CH), 3.46–3.50 (m, 1H; CH), 3.63 (brs, 1H; CH), 4.05–4.10 ppm (m, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 23.01, 24.29, 24.40, 25.37, 25.56, 25.93, 26.11, 26.15, 27.90, 28.64, 28.67, 35.56, 35.78, 44.39, 51.49, 52.76, 59.32, 140.99, 172.74 ppm; IR (film): $\tilde{\nu}$ = 1632 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{19}H_{32}N_3O$ [*M*+H]$^+$: 318.2545; found: 318.2536.

Data for 5f+5f′: Colorless oil, isolated yield 63% (152 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 0.94 (t, *J* = 7.3 Hz, 2H; CH_3, **5f′**), 1.10 (t, *J* = 7.1 Hz, 3H; CH_3, **5f**), 1.25 (s, 6H; CH_3, **5f′**), 1.35–1.36 (m, 3H; CH_2, **5f**+**5f′**), 1.44 (s, 9H; CH_3, **5f**), 1.60–1.68 (m, 6H; CH_2, **5f**+**5f′**), 1.90–2.20 (m, 1H; CH_2, **5f**+**5f′**), 2.45–2.53 (m, 1H; CH_2, **5f**+**5f′**), 2.95–3.09 (m, 1H; CH, **5f**+**5f′**), 3.46–3.54 (m, 3H; CH_2, **5f**+**5f′**), 3.69–3.73 (m, 2H; CH_2, **5f**+**5f′**), 3.84 ppm (q, *J* = 7.1 Hz, 2H; CH_3, **5f**); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 13.40, 13.42, 13.67, 15.77, 19.38, 19.94, 22.08, 24.02, 29.84, 30.00, 31.05, 32.24, 34.43, 36.57, 40.58, 42.10, 51.73, 53.11, 129.50, 144.08, 158.73, 173.55 ppm; IR (film): $\tilde{\nu}$ = 1678 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{13}H_{24}N_3O$ [*M*+H]$^+$: 238.1919; found: 238.1912.

Data for 5g: Colorless solid, isolated yield 84% (307 mg); m.p. 123.4–124.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.25 (m, 1H; CH_2), 1.50–1.61 (m, 3H; CH_2), 1.99–2.02 (m, 1H; CH_2), 2.18–2.23 (m, 1H; CH_2), 2.81–2.86 (m, 1H; CH), 3.63 (s, 3H; CH_3), 3.70 (s, 3H; CH_3), 3.86–3.93 (m, 1H; CH_2), 4.07–4.16 (m, 1H; CH_2), 6.35–6.36 (m, 1H; CH), 6.57–6.73 (m, 5H; CH), 6.99–7.07 ppm (m, 2H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.99, 20.83, 55.56 (2C), 55.61, 57.14, 60.16, 109.71, 112.23, 118.38, 120.96, 121.19, 122.25, 127.79, 129.84, 131.21, 147.37, 152.15, 155.07, 170.90, 178.65 ppm; IR (film): $\tilde{\nu}$ = 1687 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{21}H_{24}N_3O_3$ [*M*+H]$^+$: 366.1818; found: 366.1811.

Typical procedure for the preparation of 2-aminoquinazolinones 7a–f by the reaction of 2-aminobenzoate and carbodiimide

In a 25 mL of flask, $Zn(OTf)_2$ (0.05 mmol, 18 mg) was added to a 2-aminobenzoates (1.05 mmol) in benzene (5 mL). Then carbodiimide (1.00 mmol) were added to the flask, and the mixture was stirred at 80 °C for 8 h. The solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give products **7a–f**.

Data for 7a: Colorless solid, isolated yield 91% (223 mg); m.p. 97.9–98.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.3 Hz, 6H; CH_3), 1.45 (d, *J* = 7.2 Hz, 6H; CH_3), 4.24–4.33 (m, 2H; CH), 5.27 (brs, 1H; NH), 6.99–7.03 (m, 1H; CH), 7.18 (d, *J* = 7.9 Hz, 1H; CH), 7.41–7.44 (m, 1H; CH), 7.92 ppm (dd, *J* = 8.0 Hz, *J* = 1.3 Hz, 1H; CH);

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 20.14, 22.77, 43.51 (2C), 117.48, 122.07, 124.47, 126.92, 133.88, 148.83, 148.95, 163.11 ppm; IR (film): $\tilde{\nu}$ = 3367 (N–H), 1649 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{14}H_{20}N_3O$ $[M+H]^+$: 246.1606; found: 246.1600.

Data for 7b: Colorless solid, isolated yield 85% (266 mg); m.p. 112.6–113.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 5.95 (br s, 1H; NH), 7.07–7.10 (m, 1H; CH), 7.24–7.33 (m, 3H; CH), 7.41–7.43 (m, 2H; CH), 7.52–7.54 (m, 3H; CH), 7.60–7.67 (m, 4H; CH), 8.18 ppm (d, *J* = 7.8 Hz, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 118.40, 120.75, 123.63, 123.96, 125.59, 127.13, 128.83, 129.00, 130.22, 130.79, 134.51, 134.66, 137.78, 146.25, 148.46, 162.44 ppm; IR (film): $\tilde{\nu}$ = 3334 (N–H), 1675 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{20}H_{14}N_3O$ $[M+H]^+$: 314.1289; found: 314.1282. This compound has been reported previously.[20a]

Data for 7c: Colorless solid, isolated yield 89% (303 mg); m.p. 132.5–133.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.27 (s, 3H; CH_3), 2.40 (s, 3H; CH_3), 5.96 (br s, 1H; NH), 7.05–7.08 (m, 2H; CH), 7.15–7.22 (m, 3H; CH), 7.34–7.37 (m, 4H; CH), 7.45–7.47 (m, 1H; CH), 7.56–7.60 (m, 1H; CH), 8.11–8.13 ppm (m, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 20.80, 21.32, 118.32, 121.11, 123.66, 125.51, 127.13, 128.66, 129.33, 131.43, 131.77, 133.68, 134.54, 135.21, 140.40, 146.76, 148.64, 162.62 ppm; IR (film): $\tilde{\nu}$ = 3319 (N–H), 1660 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{22}H_{20}N_3O$ $[M+H]^+$: 342.1606; found: 342.1596. Single crystals of **7a** suitable for X-ray analysis were grown in ethyl acetate/hexane at room temperature for three days. This compound has been reported previously.[20b]

Data for 7d: Colorless solid, isolated yield 85% (276 mg); m.p. 132.5–133.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.3 Hz, 6H; CH_3), 1.35 (d, *J* = 7.2 Hz, 6H; CH_3), 4.13–4.24 (m, 2H; CH), 5.24 (br s, 1H; NH), 6.98 (d, *J* = 8.7 Hz, 1H; CH), 7.38 (dd, *J* = 8.7 Hz, *J* = 2.2 Hz, 1H; CH), 7.99 ppm (d, *J* = 2.1 Hz, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.17, 22.81, 43.69 (2C), 114.60, 118.84, 126.47, 129.37, 136.92, 147.94, 149.04, 162.04 ppm; IR (film): $\tilde{\nu}$ = 3414 (N–H), 1625 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{14}H_{19}BrN_3O$ $[M+H]^+$: 324.0712; found: 324.0706.

Data for 7e: Colorless solid, isolated yield 64% (251 mg); m.p. 154.0–154.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (br s, 1H; NH), 7.07–7.10 (m, 1H; CH), 7.24–7.33 (m, 3H; CH), 7.41–7.43 (m, 2H; CH), 7.50–7.54 (m, 3H; CH), 7.60–7.67 (m, 3H; CH), 8.18 ppm (d, *J* = 2.3 Hz, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.31, 119.72, 120.93, 124.22, 127.41, 128.83, 128.85, 129.42, 130.36, 130.84, 134.13, 137.45, 137.61, 146.58, 147.40, 161.20 ppm; IR (film): $\tilde{\nu}$ = 3415 (N–H), 1681 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{20}H_{15}BrN_3O$ $[M+H]^+$: 392.0398; found: 392.0393.

Data for 7f: Colorless solid, isolated yield 60% (229 mg); m.p. 161.3–164.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 5.88 (br s, 1H; NH), 7.08 (d, *J* = 7.8 Hz, 1H; CH), 7.22–7.24 (m, 1H; CH), 7.30–7.35 (m, 3H; CH), 7.45 (br s, 1H; CH), 7.55–7.57 (m, 1H; CH), 7.60–7.62 (m, 2H; CH), 7.68–7.72 (m, 2H; CH), 8.17 ppm (d, *J* = 7.8 Hz, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 118.38, 118.86, 120.93, 124.17, 124.28, 125.83, 127.22, 127.29, 129.57, 129.83, 130.85, 131.78, 134.58, 135.05, 135.51, 136.59, 138.83, 145.33, 148.05, 162.18 ppm; IR (film): $\tilde{\nu}$ = 3315 (N–H), 1667 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{20}H_{14}Cl_2N_3O$ $[M+H]^+$: 382.0514; found: 382.0509.

Typical procedure for the preparation of conjugated heterocyclic compounds 8 or 9 by the reaction of $PhI(OAc)_2$ with cyclic oxoguanidines 3a or 7b

In a 25 mL of flask, iodobenzene diacetate (0.33 mmol, 107 mg) was added to a cyclic oxoguanidines **3a** (0.30 mmol, 84 mg) or **7b** (0.30 mmol, 94 mg) in MeCN (3 mL), and the mixture was stirred at 80 °C for 2 h. The solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give products **8** or **9**.

Data for 8: Yellow solid, isolated yield 84% (72 mg); m.p. 146.9–147.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H; CH_3), 2.46 (s, 3H; CH_3), 4.63 (s, 2H; CH_2), 7.03–7.05 (m, 2H; CH), 7.32 (d, *J* = 8.3 Hz, 2H; CH), 7.55 (d, *J* = 8.1 Hz, 1H; CH), 7.70 ppm (d, *J* = 8.4 Hz, 2H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.16, 21.62, 47.41, 108.70, 119.01, 123.49, 123.67, 129.84, 129.97, 131.56, 132.38, 137.92, 142.06, 153.55, 169.96 ppm; IR (film): $\tilde{\nu}$ = 1675 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{17}H_{16}N_3O$ $[M+H]^+$: 278.1293; found: 278.1302. Single crystals of **8** suitable for X-ray analysis were grown in ethyl acetate/hexane at room temperature for three days.

Data for 9: Yellow solid, isolated yield 60% (46 mg); m.p. 158.8–159.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.31 (m, 2H; CH), 7.41–7.50 (m, 4H; CH), 7.54–7.57 (m, 2H; CH), 7.65–7.67 (m, 1H; CH), 7.83–7.88 (m, 1H; CH), 7.99–8.01 (m, 1H; CH), 8.23 (d, *J* = 8.4 Hz, 1H; CH), 8.43 ppm (dd, *J* = 7.9 Hz, *J* = 1.4 Hz, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.35, 114.45, 117.04, 119.90, 120.78, 122.48, 124.15, 125.02, 128.46, 129.38, 129.85, 130.53, 135.29, 135.36, 137.22, 142.55, 147.54, 159.70 ppm; IR (film): $\tilde{\nu}$ = 1750 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{20}H_{14}N_3O$ $[M+H]^+$: 312.1137; found: 312.1134.

Typical procedure for the preparation of compound 10 by the reaction of benzaldehyde and 2c

In a 25 mL of flask, potassium *tert*-butylate (0.33 mmol, 37 mg) was added to a benzaldehyde (0.30 mmol, 32 mg) in THF (3 mL). Then compound **2c** (0.30 mmol, 79 mg) were added to the flask, and the mixture was stirred at 60 °C for 2 h. The solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give products **10**. Yellow solid, isolated yield 72% (76 mg); m.p. 89.1–89.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.25–1.52 (m, 10H; CH_2), 1.71–1.94 (m, 8H; CH_2), 2.14–2.18 (m, 2H; CH_2), 3.76–3.82 (m, 1H; CH), 4.06–4.79 (m, 1H; CH), 4.50 (d, *J* = 7.7 Hz, 1H; NH), 6.64 (s, 1H; CH), 7.23–7.26 (m, 1H; CH), 7.36 (t, *J* = 7.7 Hz, 2H; CH), 8.07 ppm (t, *J* = 7.4 Hz, 2H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 24.71, 25.18, 25.55, 26.03, 30.78, 33.15, 50.88, 51.98, 115.94, 127.72, 128.34, 130.63, 135.88, 139.23, 156.60, 170.28 ppm; IR (film): $\tilde{\nu}$ = 3296 (N–H), 1666 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{22}H_{30}N_3O$ $[M+H]^+$: 352.2389; found: 352.2383.

Isolation of 11 from the reaction of $Zn(OTf)_2$ with ethyl nicotinate

In a 25 mL of flask, $Zn(OTf)_2$ (0.30 mmol, 109 mg) was added to an ethyl nicotinate (0.30 mmol, 32 mg) in benzene (5 mL), and the mixture was stirred at 80 °C for 1 h. After filtration, the reaction mixture was left to evaporate under a nitrogen atmosphere for five days to give single crystals of **11** suitable for X-ray analysis. Colorless solid, isolated yield 96% (199 mg); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.96 (t, *J* = 7.1 Hz, 3H; CH_3), 1.13–1.16 (m, 1H; CH_2), 1.28–1.30 (m, 2H; CH_2), 1.48–1.53 (m, 2H; CH_2), 1.84–1.87 (m, 1H; CH_2), 2.44–2.45 (m, 1H; CH_2), 2.91–2.94 (m, 1H; CH_2), 3.23–3.25 (m, 1H; CH), 3.46 (br s, 1H; NH), 3.95 ppm (q, *J* = 7.1 Hz, 2H; CH_2); ^{13}C NMR (100 MHz, C_6D_6): δ = 13.11, 23.02, 24.70, 27.97, 44.60, 57.53, 59.65, 171.94 ppm.

Isolation of 12 from the reaction of $Zn(OTf)_2$, ethyl nicotinate and DIC

In a 25 mL of flask, **11** (0.30 mmol, 109 mg) was added to DIC (0.60 mmol, 75 mg) in benzene (5 mL), and the mixture was stirred at 80 °C for 3 h. After filtration, the reaction mixture was left to evaporate under a nitrogen atmosphere to give **12**. Single crystals of **12** suitable for X-ray analysis were grown in ethyl acetate/hexane at room temperature for 3 days. Colorless solid, isolated yield 34% (131 mg); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.13$–1.15 (m, 1H; CH_2), 1.29–1.32 (m, 2H; CH_2), 1.46–1.54 (m, 12H; CH_3), 1.61–1.70 (m, 1H; CH_2), 2.01–2.07 (m, 1H; CH_2), 2.30–2.33 (m, 1H; CH_2), 3.45–3.51 (m, 1H; CH), 3.98–4.12 (m, 2H; CH_2), 4.21–4.25 (m, 1H; CH), 4.36–4.41 (m, 1H; CH), 7.87 ppm (d, $J = 8.3$ Hz, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 19.09$, 19.34, 21.58, 22.82, 23.33, 25.18, 27.59, 45.54, 48.41, 49.24, 59.63, 153.74, 171.27 ppm.

Typical procedure for the preparation of open guanidine compound 13 by the reaction of 11 with *N,N′*-diisopropylcarbodiimide (DIC)

In a 25 mL of flask, **11** (0.30 mmol, 109 mg) was added to DIC (0.60 mmol, 75 mg) in benzene (5 mL), and the mixture was stirred at 40 °C for 4 h. The solvent of the reaction mixture was evaporated under vacuum. The residue was purified by chromatography to give **13** and the byproduct **5d**. Colorless solid, isolated yield 29% (82 mg); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): $\delta = 1.18$ (d, $J = 6.2$ Hz, 6H; CH_3), 1.23 (d, $J = 6.2$ Hz, 6H; CH_3), 1.29 (t, $J = 7.5$ Hz, 3H; CH_3), 1.37–1.45 (m, 2H; CH_2), 1.58–1.60 (m, 1H; CH_2), 1.86–1.88 (m, 1H; CH_2), 2.01–2.03 (m, 1H; CH_2), 2.97–3.2 (m, 1H; CH), 3.40–3.42 (m, 1H; CH_2), 3.63–3.66 (m, 3H; 1NH, CH_2), 3.77–3.78 (m, 1H; CH_2), 3.92–3.94 (m, 1H; CH), 4.08–4.11 (m, 1H; CH_2), 4.37–4.43 ppm (m, 1H; CH); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): $\delta = 19.14$, 19.24, 20.19, 23.05, 24.87, 25.71, 27.92, 44.56, 47.60, 47.79, 59.46, 147.29, 172.66 ppm; IR (film): $\tilde{\nu} = 3335$ (C=O), 1733 cm^{-1} (C=O); HRMS: *m/z* calcd for $C_{15}H_{30}N_3O_2$ $[M+H]^+$: 284.2338; found: 284.2331.

X-ray crystallographic studies for 3b, 7c, 8, 11 and 12

Crystals of **3b**, **7c**, **8**, **11**, and **12** suitable for X-ray analysis were grown as detailed above. Data collection for **3b**, **7c**, **8**, **11** and **12** were performed at 180 K on a SuperNova diffractometer, using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Using Olex2, the structures of **3b**, **7c**, **8**, **11** and **12** were solved by use of SHELXTL program.[21a] Refinement was performed on F^2 anisotropically for all the non-hydrogen atoms by the full-matrix least-squares method with the XL refinement package. The trifluoromethyl part of **11** was disordered. The hydrogen atoms connected to N atoms in **3b**, **11** and **12** were identified according to difference electron density. Other hydrogen atoms were placed at the calculated positions and were included in the structure calculation without further refinement of the parameters. CCDC 1045541 (**3b**), CCDC 1045542 (**7c**), CCDC 1045539 (**8**), CCDC 1045543 (**11**) and CCDC 1045540 (**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif The thermal ellipsoid plots in the figures were drawn by using Ortep-3 v1.08.[21b]

Acknowledgements

This work was supported by the Natural Science Foundation of China, and the 973 Program from National Basic Research Program of China (2011CB808600).

Keywords: amino acid esters · carbodiimides · cyclic oxoguanidines · cyclization · guanylation

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Received: February 11, 2015
Published online on May 26, 2015