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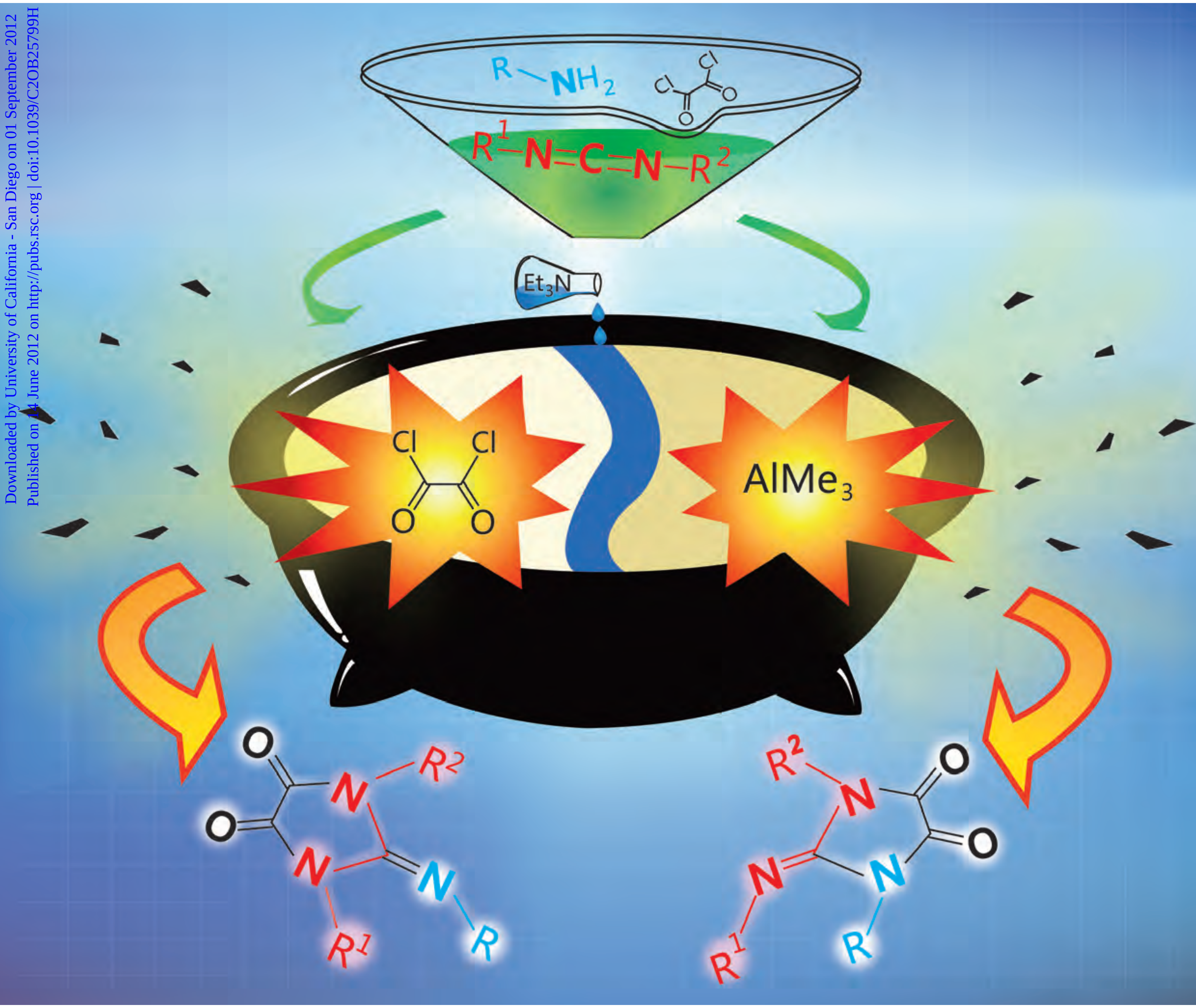

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COMMUNICATION

Metal-free synthesis of cyclic di-oxoguanidines *via* one-pot sequential transformation of amines, carbodiimides and acyl dichlorides†

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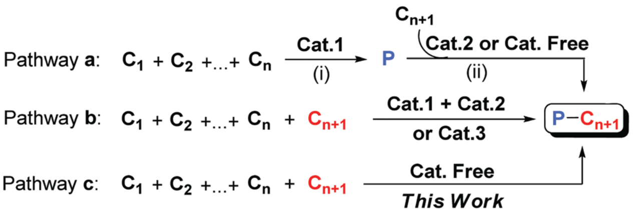
The one-pot sequential reaction of various amines, carbodiimides, and acyl dichlorides has been achieved for the first time under metal-free conditions to provide symmetric cyclic di-oxoguanidines *via* an unexpected 2,2-dichloro-imidazolidindione intermediate. Acyl dichlorides have a dual function: to serve as the third component and to activate carbodiimides. In sharp contrast, the $AlMe_3$-catalyzed sequential reaction from the same substrates gives the isomer.

Organic synthesis toward cleaner and greener chemical processes is becoming increasingly important in academia and the pharmaceutical industry because of the pressing environmental and energy problems. An ideal organic reaction should have some criteria: cheap and easily accessible starting materials, operational simplicity, high efficiency, energy-saving, catalyst-free, *etc.*[1] Transition-metal-catalyzed multicomponent synthesis or the one-pot sequential reaction gives impetus to construct efficiently some important molecules (Scheme 1, Pathway **a**, i).[2] However, subsequent incorporation of the C_{n+1} component to construct P–C_{n+1} products generally requires more than one step and needs usually the presence of the second catalyst (Pathway **a**, i and ii). The better protocol for the incorporation of the C_{n+1} component is to let the C_1 to C_{n+1} components couple in a one-pot procedure with the participation of the combined **Cat.1** and **Cat.2** or new challenging **Cat.3** (Pathway **b**). The combined **Cat.1** and **Cat.2** often suffer from catalyst incompatibility, and this often makes another catalyst deactivated in one-pot. The optimal protocol is to let the C_{n+1} component activate a certain component and lead to P–C_{n+1} products without a catalyst (Pathway **c**).

Cyclic guanidines are of great importance in biological and pharmaceutical compounds[3] or organic synthesis as base catalysts.[4] Generally, cyclic guanidines are synthesized by the following methods: (a) cyclization of guanidines;[5] (b) cyclization of vicinal diamines;[6] (c) cycloaddition of aziridines with carbodiimides;[7] (d) cycloguanidination of olefins;[8] (e) and other guanylation procedures.[9,10] These reported methods generally require metals either as catalysts or in stoichiometric amounts. Thus, a simpler and general method to synthesize cyclic guanidines remains increasingly important in modern synthetic chemistry.

We are interested in carbodiimide chemistry.[11–15] Recently we have reported two-component coupling between amines and carbodiimides to provide tri-substituted guanidines.[16] Although the metal-catalyzed two-component guanylation reaction of amines and carbodiimides is a well-established process to prepare acyclic guanidines,[16,17] how the third unknown component can be incorporated into the guanylation reaction to construct some important N-containing compounds is a challenging objective. Therefore, we envisage to conduct multicomponent coupling reactions among amines, carbodiimides, and the other components to synthesize N-containing compounds. The paper provides a new protocol: the third component can activate a certain component to make all components couple without a catalyst (Scheme 1, Pathway c). Surprisingly, we find acyl dichlorides can not only serve as the third component but also activate carbodiimides to let this sequential reaction among amines, carbodiimides and acyl dichlorides smoothly furnish cyclic di-oxoguanidines under the metal-free conditions (Scheme 2, **Type I**). In sharp contrast, the $AlMe_3$-catalyzed sequential reaction from the same substrates leads to the formation of the isomer (Scheme 2, **Type II**).



Scheme 1 Incorporation model of the C_{n+1} components. C for component, P for product, $n \geq 2$.

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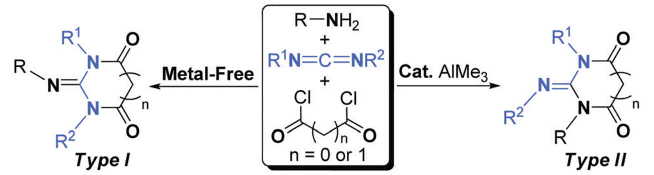
† Electronic supplementary information (ESI) available: Experimental details, X-ray data for **1e**, **1i** and **4c**, and scanned NMR spectra of all new products. CCDC 857963, 857964 and 857966. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25799h



Scheme 2 One-pot sequential transformations among amines, carbodiimides and acyl dichlorides leading to different types of cyclic dioxaguanidines.

Results and discussion

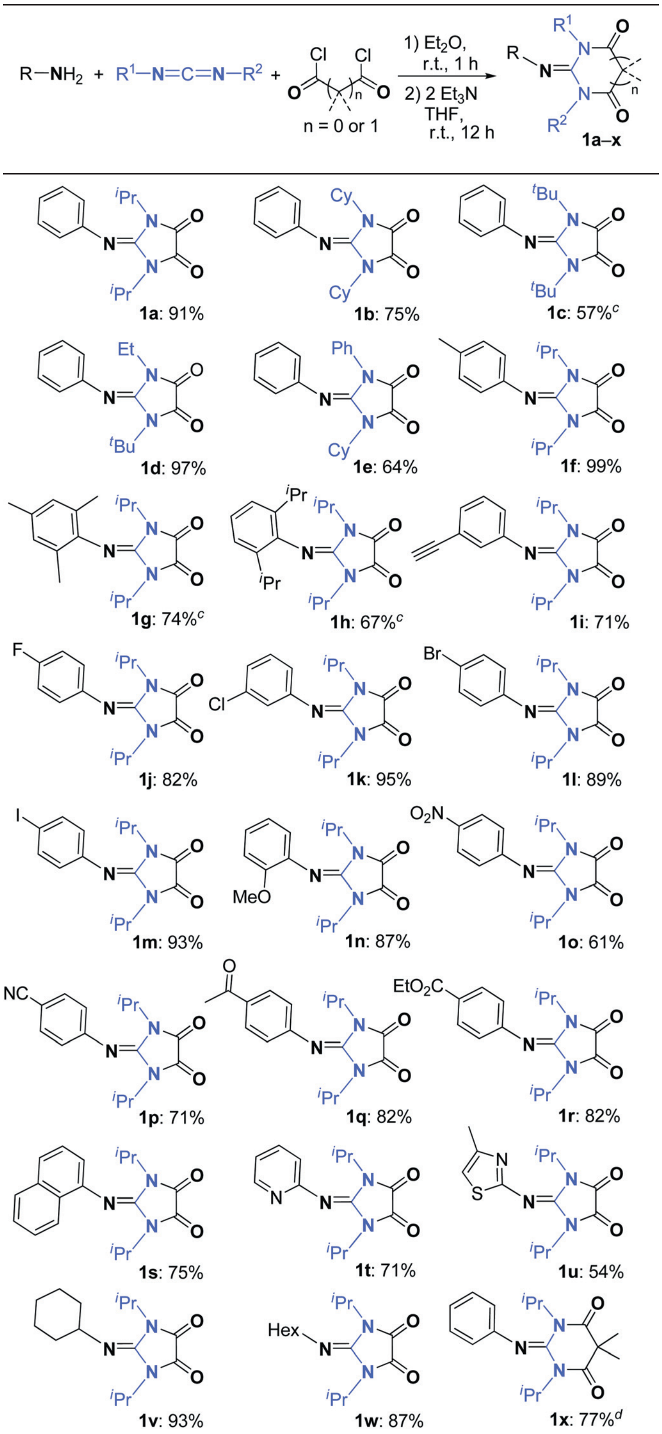
The optimized condition was established through carefully screening the reaction conditions for a metal-free sequential reaction: treatment of *N*,*N*′-diisopropylcarbodiimide (^{i}PrN═C═N^{i}Pr, DIC) with oxalyl chloride at room temperature for 1 h in Et$_2$O followed by addition of aniline, 2 equiv. of Et$_3$N and THF. Good conversion was obtained to give the desired cyclic dioxoguanidine **1a**.

Representative results obtained from the three-component reaction among various amines, carbodiimides, and acyl dichlorides are summarized in Table 1. Symmetric carbodiimides such as DIC, *N*,*N*′-dicyclohexylcarbodiimide (DCC), *N*,*N*′-di-*tert*-butylcarbodiimide and unsymmetric carbodiimides such as ^{t}BuN═C═NEt, PhN═C═NCy could all serve as suitable dual nitrogen sources to yield the corresponding cyclic guanidines **1a–e** in moderate to excellent isolated yields. A broad range of substituted anilines could be used for this three-component reaction to furnish the compounds **1a–s**. Higher temperature was required for bulky carbodiimides or anilines to yield corresponding products **1c**, **1g** and **1h**, indicating that steric hindrance on either carbodiimides or anilines would decrease the reaction rate. A variety of synthetically important functional groups, such as terminal alkyne (**1i**), halogens (F, Cl, Br, and I, **1j–m**), alkoxy (**1n**), nitro (**1o**), cyano (**1p**) and carbonyl groups (**1q,r**), were tolerated under the present conditions. Heterocyclic amines such as amino-substituted pyridine (**1t**) and thiazole (**1u**) were also applicable. In addition, aliphatic amines, such as cyclohexylamine (**1v**) and 1-hexylamine (**1w**), were also appropriate substrates. Finally, dimethyl malonyl chloride could also serve as the third component to give cyclic product **1x** in 77% yield.

The structure of **1i** was confirmed by X-ray single crystal analysis (Fig. 1). This is in agreement with the ^{1}H and ^{13}C NMR spectra in solution. The ^{1}H and ^{13}C NMR spectra of **1d** and **1e**, which resulted from the unsymmetric carbodiimides ^{t}BuN═C═NEt and PhN═C═NCy, suggested the presence of only one isomer in solution. An X-ray analysis of **1e** revealed that the bulkier NCy group is placed *trans* to the aromatic substituent around the C═N double bond (Fig. 1).

Diamines and triamines were also applicable to this three-component reaction. In the presence of 4 equiv. of Et$_3$N, the reaction of 1,4 or 1,2-diaminobenzene with 2 equiv. of ^{i}PrN═C═N^{i}Pr and oxalyl chloride gave the corresponding biguanidines **2a** and **2b** (eqn (1)). Similarly, the reaction of 1,2,4-triaminobenzene with 3 equiv. of ^{i}PrN═C═N^{i}Pr and oxalyl chloride yielded the triguanidine **2c** (eqn (2)). These multiguanidine-functionalized compounds could serve as useful templates (or ligands) for the further construction of large molecules.

Table 1 Formation of various symmetric di-oxoguanidines[a,b]



[a] Conditions: carbodiimides (1.0 mmol), acyl dichlorides (1.1 mmol) in Et$_2$O, room temperature for 1 h, then amines (1.1 mmol), Et$_3$N (2.0 mmol) and THF were added and stirred for 12 h at room temperature unless otherwise noted. [b] Isolated yield. [c] The second step was performed at 80 °C. [d] The first step required 12 h.

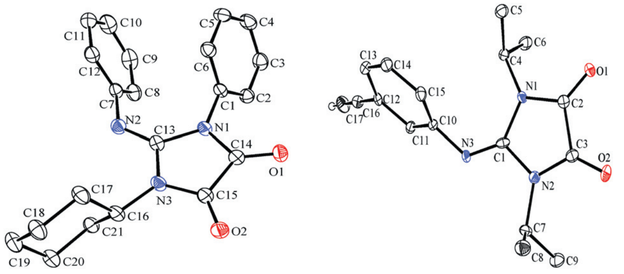
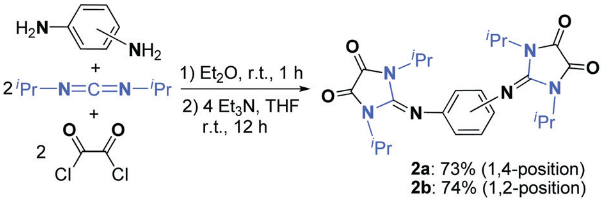
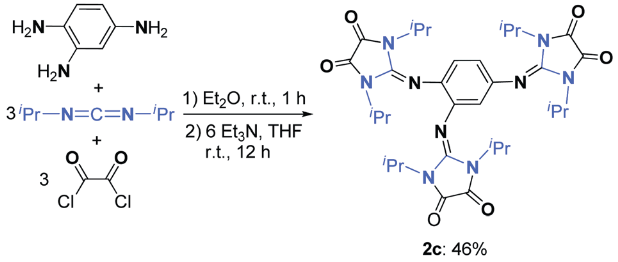


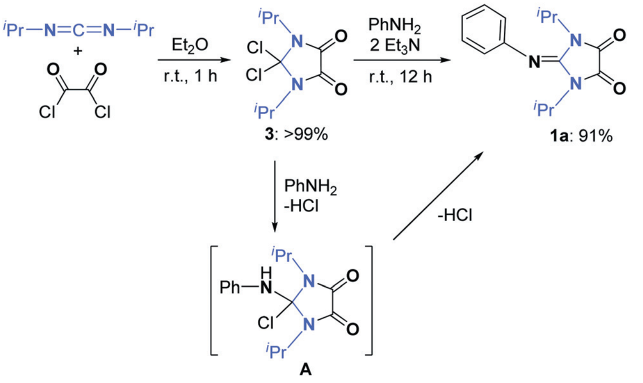
Fig. 1 ORTEP drawing of **1e** (left) and **1i** (right) with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: **1e**: C14–C15 1.526(3), C13–N1 1.419(3), C13–N2 1.258(3), C13–N3 1.405(3), C14–N1 1.378(3), C15–N3 1.356(3), C14–O1 1.205(3), C15–O2 1.204(3); **1i**: C2–C3 1.541(5), C16–C17 1.169(5), C1–N1 1.419(4), C1–N2 1.428(4), C1–N3 1.265(4), C2–N1 1.384(4), C3–N2 1.368(4), C2–O1 1.220(4), C3–O2 1.217(4).



(1)

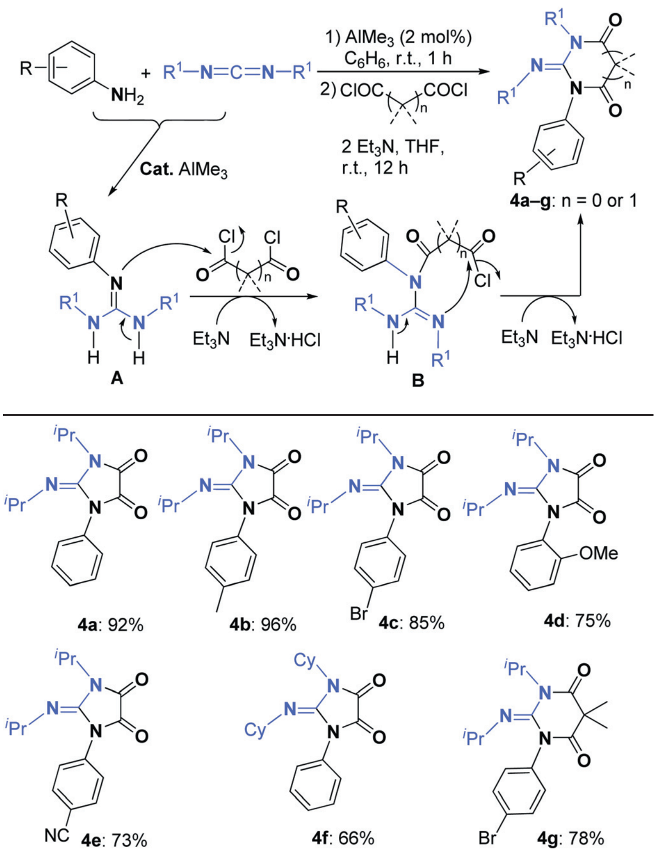


(2)



Scheme 3 Isolation and reaction of 2,2-dichloro-imidazolidindione intermediate **3**.

Table 2 Formation of unsymmetric cyclic guanidines[a,b]



[a] Conditions: carbodiimides (1.0 mmol), anilines (1.1 mmol) and $AlMe_3$ (0.02 mmol) in benzene, room temperature for 1 h, then acyl chlorides (1.1 mmol), Et_3N (2.0 mmol) and THF were added and stirred for 12 h at room temperature unless otherwise noted. [b] Isolated yield.

This sequential transformation generates much interest in how to understand the reaction process. The reaction between DIC and oxalyl chloride was first tested to afford quantitatively compound **3** at room temperature for 1 h (Scheme 3). Compound **3** was allowed to react with aniline to afford the cyclic guanidine **1a**. **1a** was detected by *in situ* NMR before quenching. The formation of **1a** could go through the intermediate **A**.

The results show that acyl dichlorides can efficiently activate the carbodiimide to provide the highly active 2,2-dichloro-imidazolidindione intermediate **3**. Formation of this active 2,2-dichloro-imidazolidindione intermediate is considered to be essential for realizing such a useful and metal-free three-component sequential transformation.

For comparison, the cyclization reaction of the pure 1,3-diisopropyl-2-phenylguanidine with oxalyl chloride in the presence of 2 equiv. of Et_3N was tried to prepare cyclic di-oxoguanidines. Surprisingly, unsymmetric cyclic guanidine **4a** was obtained. The use of a pure guanidine was not necessarily required for the above reaction. The *in situ* generated guanidines by the $AlMe_3$-catalyzed reaction of amines with carbodiimides[16b] were allowed to react with oxalyl chloride in the presence of 2 equiv. of Et_3N at room temperature for 12 h in THF providing efficiently unsymmetric cyclic guanidines **4a–f** (Table 2). Similarly, dimethyl malonyl chloride could perform the same reaction, generating **4g** as the cyclic guanidine product. All the ^1H and ^{13}C NMR spectra of **4a–g** showed two sets of signals for the ^{i}Pr, Cy groups, suggesting that the two alkyl groups in each guanidine unit should be in different environments. An X-ray analysis of **4c** revealed that the exocyclic N^{i}Pr group is placed *trans* to

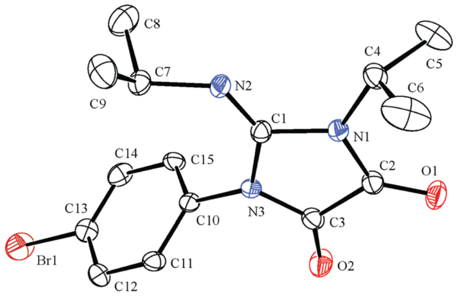


Fig. 2 ORTEP drawing of **4c** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: C2–C3 1.533(6), C1–N1 1.423(5), C1–N2 1.247(5), C1–N3 1.427(6), C2–N1 1.365(6), C3–N3 1.366(6), C2–O1 1.199(5), C3–O2 1.211(5), C13–Br1 1.910(4).

the N^{i}Pr group on the ring around the C═N double bond (Fig. 2).

The mechanism for AlMe$_3$-catalyzed formation of acyclic guanidine **A** was reported in ref. 16*b*. As shown in Table 2, one acyl group in acyl dichloride is attacked by a lone electron pair of the C═N double bond in **A**, leading to the formation of **B** by the elimination of Et$_3$N·HCl. Then **B** undergoes intramolecularly nucleophilic attack of the lone electron pair of the C═N double bond towards the other acyl group to provide the unsymmetric cyclic guanidine **4** with the second elimination of Et$_3$N·HCl.

Conclusions

In summary, the metal-free one-pot sequential coupling of various amines, carbodiimides and acyl dichlorides has been achieved for the first time, which provides a simple and general route to cyclic di-oxoguanidines *via* an unexpected 2,2-dichloro-imidazolidindione intermediate. Acyl dichlorides serve not only as the third component but also as the activator of carbodiimides. This result is quite different from the AlMe$_3$-catalyzed sequential reaction from the same substrates leading to the isomeric formation of cyclic di-oxoguanidines. Further research on application of these di-oxoguanidines is ongoing.

Acknowledgements

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References

1 (*a*) J. B. Hendrickson, *J. Am. Chem. Soc.*, 1975, **97**, 5784; (*b*) R. Noyori, *Chem. Commun.*, 2005, 1807; (*c*) T. Gaich and P. S. Baran, *J. Org. Chem.*, 2010, **75**, 4657.

2 For reviews of MCRs: (*a*) B. B. Touré and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439; (*b*) *Multicomponent Reactions*, ed. J. Zhu and H. Bienayme, Wiley-VCH, Weinheim, Germany, 2005; (*c*) J. Zhu, *Eur. J. Org. Chem.*, 2003, 1133; (*d*) A. J. von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing and M. Beller, *Chem.–Eur. J.*, 2003, **9**, 4286; for reviews of sequential reactions, see: (*e*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*f*) S. J. Hwang, S. H. Cho and S. Chang, *Pure Appl. Chem.*, 2008, **80**, 873; (*g*) J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (*h*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137; (*i*) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131.

3 (*a*) *Guanidines 2: Further Explorations of the Biological and Clinical Significance of Guanidino Compounds*, ed. A. Mori, B. D. Cohen and H. Koide, Plenum Press, New York, 1987; (*b*) *Guanidines: Historical, Biological, Biochemical and Clinical Aspects of the Naturally Occurring Guanidino Compounds*, ed. A. Mori, B. D. Cohen and A. Lowenthal, Plenum Press, New York, 1985; (*c*) R. G. S. Berlinck and M. H. Kossuga, *Nat. Prod. Rep.*, 2005, **22**, 516; (*d*) R. G. S. Berlinck, *Nat. Prod. Rep.*, 2002, **19**, 617; see also: (*e*) S. M. Weinreb, *Nat. Prod. Rep.*, 2007, **24**, 931; (*f*) A. R. Katritzky and B. V. Rogovoy, *ARKIVOC*, 2005, **5**, 49; (*g*) H. Garrido-Hernandez, M. Nakadai, M. Vimolratana, Q. Li, T. Doundoulakis and P. G. Harran, *Angew. Chem., Int. Ed.*, 2005, **44**, 765; (*h*) S. Nishimura, S. Matsunaga, M. Shibazaki, K. Suzuki, K. Furihata, R. W. M. van Soest and N. Fusetani, *Org. Lett.*, 2003, **5**, 2255.

4 (*a*) D. Leow and C.-H. Tan, *Synlett*, 2010, 1589; (*b*) R. Lee, X. Lim, T. Chen, G. K. Tan, C.-H. Tan and K.-W. Huang, *Tetrahedron Lett.*, 2009, **50**, 1560; (*c*) D. Leow and C.-H. Tan, *Chem.–Asian J.*, 2009, **4**, 488; (*d*) J. Shen and C.-H. Tan, *Org. Biomol. Chem.*, 2007, **6**, 3229.

5 (*a*) M. Kim, J. V. Mulcahy, C. G. Espino and J. Du Bois, *Org. Lett.*, 2006, **8**, 1073; (*b*) G. Büchi, A. D. Rodriguez and K. Yakushijin, *J. Org. Chem.*, 1989, **54**, 4494.

6 (*a*) V. J. Cee and N. S. Downing, *Tetrahedron Lett.*, 2006, **47**, 3747; (*b*) U. Heinelt, D. Schultheis, S. Jäger, M. Lindenmaier, A. Pollex and H. S. G. Beckmann, *Tetrahedron*, 2004, **60**, 9883; (*c*) Y. Yu, J. M. Ostresh and R. A. Houghten, *J. Org. Chem.*, 2002, **67**, 3138; (*d*) T. Isobe, K. Fukuda, T. Tokunaga, H. Seki, K. Yamaguchi and T. Ishikawa, *J. Org. Chem.*, 2000, **65**, 7774; (*e*) S. Matsunaga, R. E. Moore, W. P. Niemczura and W. W. Carmichael, *J. Am. Chem. Soc.*, 1989, **111**, 8021; (*f*) E. H. Schweizer, F. Märki and G. Rihs, *J. Med. Chem.*, 1983, **26**, 970; (*g*) C. M. Baltzer and C. G. McCarty, *J. Org. Chem.*, 1973, **38**, 155.

7 (*a*) D. C. D. Butler, G. A. Inman and H. Alper, *J. Org. Chem.*, 2000, **65**, 5887; (*b*) J.-O. Baeg, C. Bensimon and H. Alper, *J. Am. Chem. Soc.*, 1995, **117**, 4700.

8 (*a*) B. Zhao, H. Du and Y. Shi, *Org. Lett.*, 2008, **10**, 1087; (*b*) K. Muñiz, J. Streuff, C. H. Hövelmann and A. Núñez, *Angew. Chem., Int. Ed.*, 2007, **46**, 7125.

9 (*a*) H. Shen, Y. Wang and Z. Xie, *Org. Lett.*, 2011, **13**, 4562; (*b*) D. S. Ermolat’ev, J. B. Bariwal, H. P. L. Steenackers, S. C. J. De Keersmaecker and E. V. Van der Eychen, *Angew. Chem., Int. Ed.*, 2010, **49**, 9465; (*c*) X. Wang, S. Dixon, N. Yao, M. J. Kurth and K. S. Lam, *Tetrahedron Lett.*, 2005, **46**, 5747.

10 A two-step three-component synthesis from amines, carbodiimides and acyl dichlorides forming cyclic guanidines was mentioned, in which only three examples were characterized by melting point and elemental analysis without any NMR data, see: G. Zinner and R. Vollrath, *Chem. Ber.*, 1970, **103**, 766.

11 Selected reviews of carbodiimide chemistry: (*a*) M. Nishiura and Z. Hou, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 595; (*b*) T. Suzuki, W.-X. Zhang, M. Nishiura and Z. Hou, *J. Synth. Org. Chem., Jpn.*, 2009, **67**, 451; (*c*) H. Shen and Z. Xie, *J. Organomet. Chem.*, 2009, **694**, 1652; (*d*) W.-X. Zhang and Z. Hou, *Org. Biomol. Chem.*, 2008, **6**, 1720; (*e*) A. Williams and I. T. Ibrahim, *Chem. Rev.*, 1981, **81**, 589.

12 Selected examples of addition of nucleophiles to carbodiimides: (*a*) Y. Wang, W.-X. Zhang, Z. Wang and Z. Xi, *Angew. Chem., Int. Ed.*, 2011, **50**, 8122; (*b*) D. Li, Y. Wang, W.-X. Zhang, S. Zhang, J. Guang and Z. Xi, *Organometallics*, 2011, **30**, 5278; (*c*) W.-X. Zhang, M. Nishiura, T. Mashiko and Z. Hou, *Chem.–Eur. J.*, 2008, **14**, 2167; (*d*) X. Xu, J. Gao, D. Cheng, J. Li, G. Qiang and H. Guo, *Adv. Synth. Catal.*, 2008, **350**, 61; (*e*) W.-X. Zhang, M. Nishiura and Z. Hou, *Chem. Commun.*, 2006, 3812; (*f*) W.-X. Zhang, M. Nishiura and Z. Hou, *J. Am. Chem. Soc.*, 2005, **127**, 16788.

13 Selected examples of cycloaddition of carbodiimides: (*a*) F. Wang, S. Cai, Q. Liao and C. Xi, *J. Org. Chem.*, 2011, **76**, 3174; (*b*) G. Shen and W. Bao, *Adv. Synth. Catal.*, 2010, **352**, 981; (*c*) R. T. Yu and T. Rovis, *J. Am. Chem. Soc.*, 2008, **130**, 3262; (*d*) A. Volonterio and M. Zanda, *Org. Lett.*, 2007, **9**, 841; (*e*) T. Saito, K. Sugizaki, T. Otani and T. Suyama, *Org. Lett.*, 2007, **9**, 1239; (*f*) X. Xu, D. Cheng, J. Li, H. Guo and J. Yan, *Org. Lett.*, 2007, **9**, 1585; (*g*) H. Li, J. L. Petersen and K. K. Wang, *J. Org. Chem.*, 2003, **68**, 5512; (*h*) M. Schmittel, D. Rodríguez and J.-P. Steffen, *Angew. Chem., Int. Ed.*, 2000, **39**, 2152.

14 For examples of rearrangement of carbodiimides, see: (*a*) Y. Wang, Y. Chi, W.-X. Zhang and Z. Xi, *J. Am. Chem. Soc.*, 2012, **134**, 2926; (*b*) C. Wentrup, *Acc. Chem. Res.*, 2011, **44**, 393; (*c*) D. Kvaskoff, M. Vosswinkel and C. Wentrup, *J. Am. Chem. Soc.*, 2011, **133**, 5413;

(*d*) Z. Wang, Y. Wang, W.-X. Zhang, Z. Hou and Z. Xi, *J. Am. Chem. Soc.*, 2009, **131**, 15108.

15 For examples of carbodiimide metathesis: (*a*) T.-G. Ong, G. P. A. Yap and D. S. Richeson, *Chem. Commun.*, 2003, 2612; (*b*) R. L. Zuckerman and R. G. Bergman, *Organometallics*, 2000, **19**, 4795.

16 (*a*) D. Li, J. Guang, W.-X. Zhang, Y. Wang and Z. Xi, *Org. Biomol. Chem.*, 2010, **8**, 1816; (*b*) W.-X. Zhang, D. Li, Z. Wang and Z. Xi, *Organometallics*, 2009, **28**, 882.

17 Selected examples: (*a*) J. Koller and R. G. Bergman, *Organometallics*, 2010, **29**, 5946; (*b*) J. Romero-Fernández, F. Carrillo-Hermosilla, A. Antiñolo, C. Alonso-Moreno, A. M. Rodríguez, I. López-Solera and A. Otero, *Dalton Trans.*, 2010, **39**, 6419; (*c*) M. R. Crimmin, A. G. M. Barrett, M. S. Hill, P. B. Hitchcock and P. A. Procopiou, *Organometallics*, 2008, **27**, 497; (*d*) Z. Du, W. Li, X. Zhu, F. Xu and Q. Shen, *J. Org. Chem.*, 2008, **73**, 8966; (*e*) Q. Li, S. Wang, S. Zhou, G. Yang, X. Zhu and Y. Liu, *J. Org. Chem.*, 2007, **72**, 6763; (*f*) W.-X. Zhang, M. Nishiura and Z. Hou, *Chem.–Eur. J.*, 2007, **13**, 4037; (*g*) T.-G. Ong, J. S. O'Brien, I. Korobkov and D. S. Richeson, *Organometallics*, 2006, **25**, 4728; (*h*) H. Shen, H.-S. Chan and Z. Xie, *Organometallics*, 2006, **25**, 5515; (*i*) F. Montilla, D. del Río, A. Pastor and A. Galindo, *Organometallics*, 2006, **25**, 4996; (*j*) W.-X. Zhang, M. Nishiura and Z. Hou, *Synlett*, 2006, 1213; (*k*) T.-G. Ong, G. P. A. Yap and D. S. Richeson, *J. Am. Chem. Soc.*, 2003, **125**, 8100.