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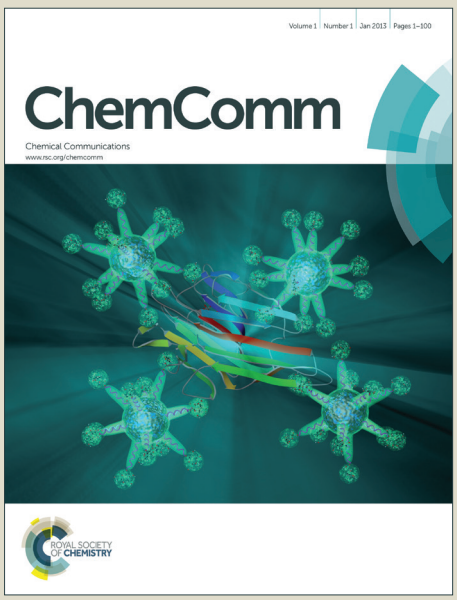

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Synthesis of carbonyl 2-amino-pyrimidines via tandem regioselective heterocyclization of 1,3-diynes with guanidine and selective oxidation

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A highly efficient one-pot approach for the synthesis of carbonyl 2-amino-pyrimidines from 1,3-diynes and guanidine in the presence of Cs_2CO_3 and DMSO has been described. In these reactions, 1,3-diynes act as precursor of buta-1,2,3-trienes and guanidine serves as a N-C=N source for the construction of pyrimidines. This methodology proves to be a tandem regioselective heterocyclization of 1,3-diyne with guanidine and selective oxidation with DMSO.

Pyrimidines are recognized as extremely important heterocycles in bioorganic and medicinal chemistry owing to their biological properties and therapeutical importance.[1] Amino-pyrimidine fragment widely emerges in naturally occurring compounds and biological molecules, especially in DNA and RNA.[1c,1e] Among these pyrimidines, 2-amino-pyrimidine derivatives serve as commercial drugs such as antitumour (Meridianins)[2], antimicrobial (Diaveridine)[3], decrease the cholesterol level (Rosuvastatin)[4], and treatment of anemia (Peroyl-*L*-glutamic)[5] (Figure 1).

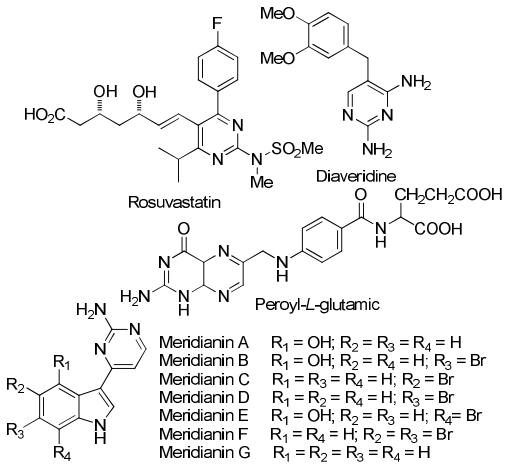
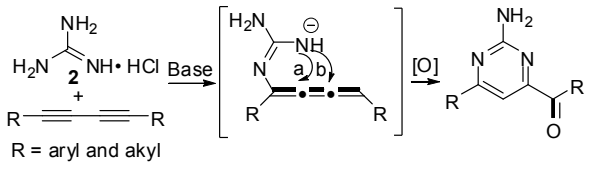


Fig. 1 Representative 2-aminopyrimidine derivatives.

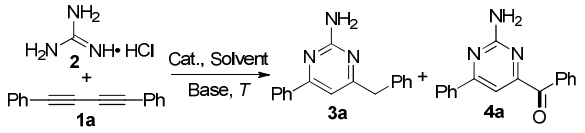
Conventionally, the construction of 2-aminopyrimidines relies on condensation of guanidines with 1,3-dicarbonyl derivatives[6], ynones[7] or α,β-unsaturated ketones[8]. These syntheses often suffer from the drawbacks such as multistep reactions, harsh reaction conditions, low efficiency and the use of special starting materials.[1e, 6-8] Therefore, the significance of straightforward, efficient and green methods for the synthesis of 2-amino-pyrimidines can scarcely be overestimated. 1,3-Diyenes are versatile intermediates for the synthesis of hetero (*N*, *O* and *S*)-cycles.[9] However, 1,3-diyenes are often applicable for [4+1] annulations, which gave five-membering heterocycles. Only one example for [4+2] heterocyclization of 1,3-diyenes with benzylamine under copper catalysis was reported by Chalk.[10] In our previous paper,[11] we found that 1,3-diynes may be a precursor of substituted buta-1,2,3-trienes. Thus, we speculated that [3+3] heterocyclization of 1,3-diynes with guanidine may occur to provide methylene-substituted 2-amino pyrimidines, meanwhile the methylene may be oxidized in one-pot (Scheme 1). The direct oxidation of C–H bonds is one of the powerful methods to form complex carbonyl compounds.[12] The oxidation of the aliphatic group that directly attached to the heteroaromatic ring has attracted great attention during the latest decade.[13] To the best of our knowledge, the synthesis of carbonyl 2-amino pyrimidines through a tandem [3+3] heterocyclization of 1,3-diynes with guanidine and oxidation has not been investigated yet. In this paper, we report such a reaction in the presence of Cs_2CO_3 and DMSO, which regioselectively affords carbonyl 2-amino-pyrimidines.



Scheme 1 Regioselective heterocyclization and oxidation.

To explore our hypothesis, we initiated our studies with a reaction of 1,4-diphenylbuta-1,3-diyne **1a** with guanidine hydrochloride **2** in the presence of CuCl[10] and Cs_2CO_3 in dimethyl sulfoxide (DMSO) at 120 °C for 12 h. To our delight, a formation of 4-benzyl-6-phenylpyrimidin-2-amine **3a** and (2-amino-6-phenylpyrimidin-4-yl)(phenyl)methanone **4a**[14] was indeed observed; five-member ring heterocycles, 4-phenyl-5-(phenylethynyl)-1*H*-imidazol-2-amine, and other heterocycles were not obtained (Table 1, entry 1). Other transition-metal species such as $Pd(OAc)_2$ was probed and it gave a similar result (entry 2). These results revealed that 2-amino-pyrimidine **3a** was formed, followed by an oxidation of methylene of **3a** with DMSO[15], to produce **4a**. It is of interest to note that AgOAc only afforded the desired product **4a** in 60% yield (entry 3). More significantly, this reaction gave a 99% yield of **4a** in the absence of transition-metal catalyst (entry 4). Inspirited by these outcomes, a variety of solvents such as toluene, dioxane and 1,2-dichloroethane (DCE) was screened and they were ineffective (entries 5–7). Thus, DMSO is not only the optimum solvent but also an oxidant in this reaction (entry 4). The nature of bases has a crucial impact on the reactions. Consequently, a series of bases including K_2CO_3, K_3PO_4, and potassium *tert*-butoxide (*t*-BuOK) was evaluated. K_2CO_3 and K_3PO_4 resulted in a mixture of **3a** and **4a** (entries 8 and 9). Either Cs_2CO_3 or *t*-BuOK gave rise to **4a** in excellent yields (entry 10). The reaction was also carried out at 110 °C and it gave a 67% yield of **4a** (entry 11). Note that other heterocyclic compounds were not observed in all cases.

Table 1 Screening the reaction conditions[a]

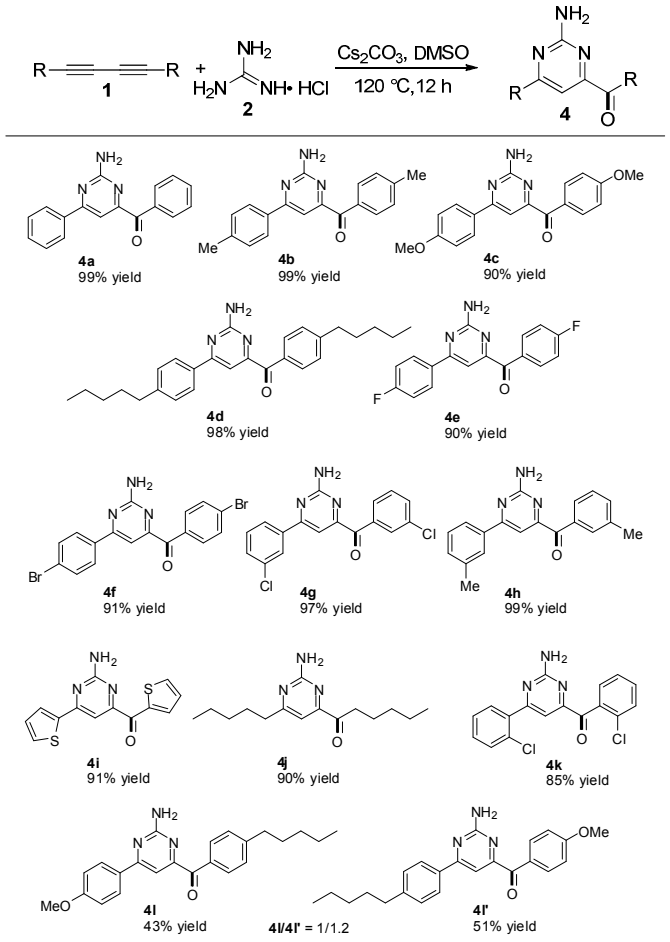


Entry	Catalyst	Solvent	Additive	Temp (°C)	Yield[b] (%)	
					3a	4a
1	CuCl	DMSO	Cs_2CO_3	120	45	31
2	$Pd(OAc)_2$	DMSO	Cs_2CO_3	120	41	20
3	AgOAc	DMSO	Cs_2CO_3	120	-	61
4	-	DMSO	Cs_2CO_3	120	-	99
5	-	Toluene	Cs_2CO_3	120	-	-
6	-	Dioxane	Cs_2CO_3	120	-	-
7	-	DCE	Cs_2CO_3	120	-	-
8	-	DMSO	K_2CO_3	120	19	78
9	-	DMSO	K_3PO_4	120	24	72
10[c]	-	DMSO	*t*-BuOK	120	-	90
11	-	DMSO	Cs_2CO_3	110	-	67

[a]Reaction conditions: Transition–metal catalyst (5 mol%) for entries (1–3), 1,3-diyne **1a** (0.2 mmol), guanidine hydrochloride **2** (0.24 mmol) and base (0.40 mmol) in solvent (2 mL) in a sealed tube for 12 h. [b]Isolated yield. [c]1 mmol of *t*-BuOK was used.

Upon using the optimized reaction conditions shown in entry 4 of Table 1, the scope and generality of varying 1,3-diynes **1** with guanidine hydrochloride **2** was further examined. 1,3-Diynes **1a** and 1,3-diynes **1b–h** bearing electron-rich (e.g., *p*-Me, *p*-MeO, *p*-pent and *m*-Me) or electron-poor group (e.g., *p*-F, *p*-Br, *m*-Cl and *o*-Cl) on the phenyl ring afforded **4b–h**, **k** in good to excellent yields. Notably, **1b**, **1d**, and **1h** occurred the selective oxidation of methylene which directly attached on the aromatic ring; and the other aliphatic group (e.g., Me and pentyl) on the phenyl ring was not oxidated in this process. 2-Thienyl substituted 1,3-diyne **1i** provided the corresponding product **4i**[16] in a 91% yield. Moreover, aliphatic substrate such as pentadeca-6,8-diyne **1j** worked well and it gave a 90% yield of **4j**. Unsymmetrical 1,3-diyne **1l** was examined and it gave a mixture of **4l** and **4l'** (**4l**/**4l'** = 1/1.2) in total 94% yields.

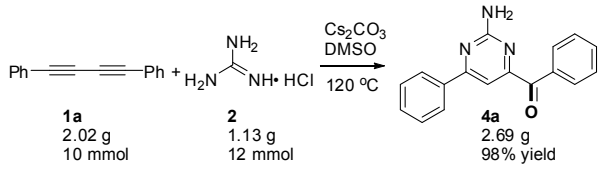
Table 2 Scope of 1,3-diynes **1** with guanidine hydrochloride **2**[a-b]



[a]Reaction conditions: 1,3-diynes **1** (0.2 mmol), guanidine hydrochloride **2** (0.24 mmol) and Cs_2CO_3 (0.4 mmol) in DMSO (2 mL) in a sealed tube for 12 h. [b]Isolated yield.

The amino group on the aromatic ring can undergo various transformations and it shows the great tolerance in all cases. Compounds **4a–i** are structural analogue of emmacin[17] and they may exhibit good bioactive properties. Note that other heterocyclic compounds were not observed in all cases. Both **3** and **4** could be isolated from DMSO by a dilution with brine, extraction with AcOEt, and silica gel chromatography, respectively.

To test the synthetic utility of this method, **4a** was prepared on a gram scale. For example, 1,3-diyne **1a** (10 mmol, 2.02 g) and guanidine hydrochloride **2** (12 mmol, 1,13 g) were tested under the optimal conditions, and it gave **4a** (2.69 g) in 98% yield (Scheme 2). The molecular structures of **4a**[14] were established by its X-ray crystallographic analysis (Figure 2).



Scheme 2 Gram-scale synthesis of **4a**.

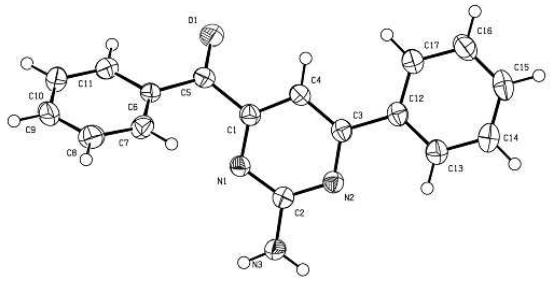
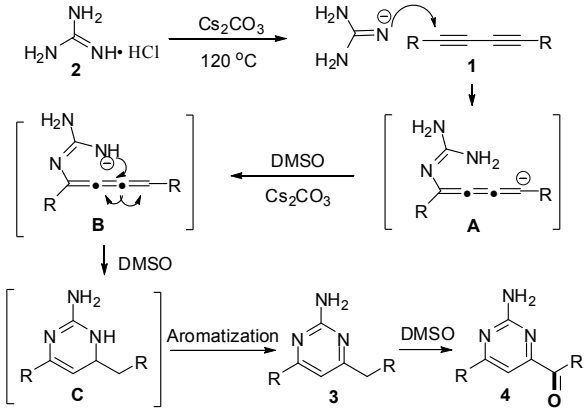


Fig. 2 Molecular structures of **4a**.

The controlled experiments were conducted under the optimized conditions: (i) the component solvent (2 mL of $(CD_3)_2SO$ and 50 μL of H_2O) was used, a di-deuterated methylene (CD_2/CH_2 = 9/1) and a deuterated pyrimidine ring (D/H = 1/1) both were obtained in the course of the reaction (see: ^1H NMR spectra in SI); in contrast (ii) the component solvent (2 mL of $(CH_3)_2SO$ and 50 μL of D_2O) was employed and no deuterated products were observed; and (iii) **3a** (0.2 mmol, 52.2 mg) was converted into **4a** (50.1 mg, 91% yield).

A plausible mechanism was proposed and illustrated in Scheme 3. The treatment of guanidine hydrochloride **2** with Cs_2CO_3 in DMSO at 120 °C forms an anion of guanidine, the addition of which to 1,3-dyine **1** affords an anion of buta-1,2,3-triene **A**. A protonation of **A** with DMSO, followed by a deprotonation in the presence of Cs_2CO_3 gives **B**. A heterocyclization of **B** undergoes, followed by quenching with DMSO to form **C**. The aromatization reaction of **C** occurs to provide **3**, the latter is oxidised with DMSO[15] to produce **4** (Scheme 3).



Scheme 3 The plausible mechanism of the present reaction.

Conclusions

In conclusion, we have developed the tandem hetero-cyclization of 1,3-diynes with guanidine hydrochloride and oxidation with DMSO in the presence of Cs_2CO_3, which selectively produced carbonyl 2-amino-pyrimidines in excellent yields. This is the first example for the synthesis of carbonyl 2-amino-pyrimidines from 1,3-diynes and guanidine.

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Notes and references

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1 For selective books and reviews see: (a) A. W. Erian, *Chem. Rev.* 1993, **93**, 1991; (b) K. Undheim and T. Benneche, *in Comprehensive Heterocyclic Chemistry II*, Vol. 6 (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven and A. McKillop), Pergamon, Oxford, 1996, pp. 93; (c) J. A. Joule and K. Mills, *in Heterocyclic Chemistry*, 4th ed. Blackwell, Cambridge, 2000, pp. 194; (d) M. D. Hill and M. Movassaghi, *Chem.- Eur. J.* 2008, **14**, 6836; (e) E. V. Koroleva, K. N. Gusak and Z. V. Ignatovich, *Russian Chem. Rev.* 2010, **79**, 655; For selective examples, see: (f) I. M. Lagoja, *Chem. Biodiversity* 2005, **2**, 1; (g) J. P. Michael, *Nat. Prod. Rep.* 2005, **22**, 627; (h) M. Movassaghi and M. D. Hill, *J. Am. Chem. Soc.* 2006, **148**, 14244; (i) M. Movassaghi and M. D. Hill, *Nat. Protoc.* 2007, **2**, 2018.

2 (a) S. R. Walker, E. J. Carter, B. C. Huff and J. C. Morris, *Chem. Rev.* 2009, **109**, 3080; (b) P. M. Pauletti, L. S. Cintra, C. G. Braguine, A. A. Da Silva Filho, M. L. A. Silva, W. R. Cunha and A. H. Januário, *Marine Drugs* 2010, **8**, 1526; (c) E. Rossignol, E. Debiton, D. Fab-bro, P. Moreau, M. Prudhomme and F. Anizon, *Anti-Cancer Drugs* 2010, **19**, 789; (d) S. B. Bharate, R. R. Yadav, S. Battula and R. A. Vishwakarma, *Med. Chem.* 2012, **12**, 618; (e) S. B. Bharate, R. R. Yadav and R. A. Vishwakarma, *Med. Chem.* 2013, **9**, 152; (f) K. Li, L. R. McGee, B. Fisher, A. Sudom, J. Liu, S. M. Rubenstein, M. K. Anwer, T. D. Cushing, Y. Shin, M. Ayres, F. Lee,; J. Eksterowicz, P. Faulder, B. Waszkowycz, O. Plotnikova, E. Farrelly, S.-H. Xiao, G. Chen and Z. Wang, *Bioorg. Med. Chem. Lett.* 2013, **23**, 1238.

3 For selective examples, see: (a) B. Roth, E. A. Folco, G. H. Hitchings and S. R. M. Bushby, *J. Med. Chem.*, 1962, **5**, 1103; (b) P. Stenbuck, R. Baltzly and H. M. Hood, *J. Org. Chem.*, 1963, **28**, 1983; (c) N. I. Khromov-Borisov and I. I. Tikodeeva, *Pharm. Chem. J.* 1970, **6**, 18; (d) M. Hooffer, E. Grunberg, M. Mi-trovic and A. Brossi, *J. Med. Chem.*, 1971, **14**, 462.

4 For the application of rosuvastatin, see: (a) M. Watanabe, H. Koike, T. Ishiba, T. Okada, S. Sea and K. Hirai, *Bioorg. Med. Chem.* 1997, **5**, 437; (b) M. Davidson, P. Ma, E. A. Stein, A. M. Gotto, A. Raza, R. Chitra and H. Hutchinson, *Am. J. Cardiol.* 2002, **89**, 268; (c) J. Quirk,

M. Thornton and P. Kirkpatrick, *Nat. Rev. Drug Discovery* 2003, **2**, 769; (d) N. S. Culhane, S. L. Lettieri and J. R. Skae, *Pharmacotherapy* 2005, **25**, 990; and literature cited therein; (e) N. Andrushko, V. Andrushko, G. Konig, A. Spannenberg and A. Berner, *Eur. J. Org. Chem.* 2008, 847.

5 For selective reviews see: A. T. Balaban, D. C. Oniciu and A. Katritzky, *Chem. Rev.* 2004, **104**, 2777; and references cited therein.

6 For selective examples, see: (a) W. Wendelin, K. Schermanz, K. Schweiger and A. Fuchsgruber, *Monatsh. Chem*. 1983, **114**, 1371; (b) A. W. Erian, *Chem. Rev.* 1993, **93**, 1991.

7 For selective examples, see: (a) M. C. Bagley, D. D. Hughes, P. H. Taylor, *Synlett*, 2003, 259; (b) A. S. Karpov and T. J. J. Müller, *Org. Lett.*, 2003, **5**, 3451; (c) A.S. Karpov and T. J. J. Müller, *Synthesis*, 2003, 2815; (d) D.M. D'Souza and T. J. J. Müller, *Nat. Protoc.*, 2008, **3**, 1660; (e) S. Santra, K. Dhara, P. Ranjan, P. Bera, J. Dash and S. K.Mandal, *Green Chem.*, 2011, **13**, 3238.

8 (a) S. M. S. Chauhan and A. H. Junjappa, *Tetrahedron* 1979, **32**, 1779; (b) A. L. Marzinzik and E. R. Felder, *J. Org. Chem.* 1998, **63**, 724; (c) S. Zhu, S. Shi, S. W. Gerritz and M. J. J. Sofia, *Comb. Chem.* 2003, **63**, 205; (d) P. Bannwarth, A. Valleix, D. Grée and R. Grée, *J. Org. Chem.* 2009, **74**, 4646.

9 For a recent review, see: W. Shi and A. W. Lei, *Tetrahedron Lett.* 2014, **55**, 2763.

10 CuCl was used as catalyst for the heterocyclization of 1,3-diynes, see: A. J. Chalk, *Tetrahedron Lett.* 1972, **13**, 3487.

11 (a) L. Ming, J. L. Tang and X. M. Zhao, *Synthesis*, 2014, **46**, 2499; (b) L. Zhang and X. M. Zhao, *Org. Lett.* 2015, **17**, 184.

12 (a) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.* 2005, **105**, 232; (b) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.* 2011, **111**, 1780; (c) A. N. Campbell and S. S. Stahl, Acc. *Chem. Res.* 2012, **45**, 851; (d) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.* 2012, **41**, 3381; (e) S. E. Allen, R. R. Walvoord, R. PadillaSalinas and M. C. Kozlowski, *Chem. Rev.* 2013, **113**, 6234.

13 (a) J. De Houwer, K. A. Tehrani and B. U. W. Maes, *Angew. Chem. Int. Ed.* 2012, **51**, 2745; (b) Y. Wang, F. Zhang and S. Chiba, *Synthesis* 2012, **44**, 1526 ; (c) M. Itoh, K. Hirano, T. Satoh and M. Miura, *Org. Lett.* 2014, **16**, 2050.

14 The molecular structure of **4a** was supported by their X-ray crystallographic analysis, see: CCDC 1042293 (**4a**) 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.

15 DMSO used as an oxidant was reported, for selective examples, see: (a) Y. Jinbo, H. Kondo, M. Taguchi, F. Sakamoto and G. Tsukamoto, *J. Org. Chem.* 1994, **59**, 6057; (b) S. Biswas and S. Batra, *Eur. J. Org. Chem.* 2012, 3492; (c) M. Raghavender Reddy, N. Nageswara Rao, K. Ramakrishna and H. M. Meshram, *Tetrahedron Lett.* 2014, **55**, 4758. For reviews, see: (d) W. W. Epstein and F. W. Sweat, *Chem. Rev.* 1967, **67**, 247; (e) H. D. Martin, A.Weise, and H.-J. Niclas, *Angew. Chem., Int. Ed.* 1967, **6**, 318; (f) A. J. Mancuso, and D. Swern, *Synthesis* 1981, 165; (g) T. T. Tidwell, *Synthesis* 1990, 857; (h) S. N. Kilenyi, Oxidation of Carbon−Halogen Bonds. In *Comprehensive Organic Synthesos*; Trost, B. M., Fleming, I., Ed.; Pergamon: Oxford, 1991.

16 The analogue of **4i** as the antimicrobials was reported, see: V. Kanagarajan, J. Thanusu and M. Gopalakrishnan, *Eur. J. Med. Chem.* 2010, **45**, 1583.

17 For selective example, see: (a) E. E. Wyatt, S. Fergus, W. R. J. D. Galloway, A. Bender, D. J. Fox, A. T. Plowright, A. S. Jessiman, M. Welch and D. R. Spring, *Chem. Commun.*, 2006, 3296; (b) E. E. Wyatt, W. R. J. D. Galloway, G. L. Thomas, M. Welch,; O. Loiseleur, A. T. Plowrightd and D. R. Spring, *Chem. Commun.*, 2008, 4962.