ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 7571–7573

www.rsc.org/chemcomm

COMMUNICATION

Cascade annulation of malonic diamides: a concise synthesis of polycyclic pyrroloindolines†

Feng Fan,[a] Weiqing Xie*[b] and Dawei Ma*[ab]

Received 1st May 2012, Accepted 7th June 2012
DOI: 10.1039/c2cc33129b

A concise synthesis of polycyclic pyrroloindolines from simple malonic diamides *via* an intramolecular oxidative coupling/condensative cyclization cascade process is reported. The reaction provides an efficient method to construct polycyclic pyrroloindolines in good to excellent yields, which should be useful in the synthesis of natural products and pharmaceutical molecules.

Pyrroloindolines have a fused indole framework that is widely found in both natural products and medicinal molecules with promising biological activities.[1] Due to their structural complexity and biological activities, numerous methods have been developed for the synthesis of such a motif.[2] Besides simple pyrroloindoline alkaloids such as physostigmine,[3] polycyclic pyrroloindolines (*e.g.* minfiensine[4]) have attracted much more attention from the chemical community due to the synthetic challenges posed by their structural complexity. To establish polycyclic pyrroloindoline scaffolds, multiple synthetic steps are usually needed,[3,4] which prevents them from being applied in diverse synthesis. From the standpoint of medicinal chemistry, a simple synthetic method for the synthesis of a collection of natural product-like molecules is a powerful tool in the search for biologically active compounds.[5] Taking into consideration both atom economy and synthetic efficiency in chemical synthesis, a concise and practical approach for the construction of polycyclic pyrroloindolines with chemical diversity is still highly desirable for chemical biology and medicinal chemistry research.

Oxidative coupling is an important method for C–C bond formation.[6,7] Although extensive studies have been devoted to oxidative homocoupling,[6] oxidative heterocoupling has received little attention due to competitive homocoupling side-reactions.[7] In consequence, oxidative coupling has rarely been applied in the total synthesis of natural products until the recent work from the Baran group,[8] Overman group,[9] our group,[10] and others.[11]

As a part of our ongoing program on the intramolecular oxidative coupling of tryptamine derived precursors, we have already applied this strategy in the total synthesis of the communesin family of alkaloids.[10] To evaluate the feasibility of designing a cascade reaction initiating with oxidative coupling, we recently reported an efficient synthesis of polycyclic spiroindolines from simple tryptamine keto-amides *via* an oxidative coupling/condensative cyclization cascade process.[12] The reaction took advantage of the nucleophilicity of the oxygen atom of the enolate to facilitate capture of the imine resulting from oxidative coupling and enabled the construction of tetracyclic spiroindoline in a one-pot reaction.

Since an increasing number of polycyclic pyrroloindoline natural products have been isolated with potent biological activities,[2] we turned our attention to designing a new cascade reaction to construct polycyclic pyrroloindoline scaffolds, which would provide quick access to a series of polycyclic pyrroloindolines **4** from malonic diamides **1** (Fig. 1). When malonic diamide **1** is subjected to the cascade reaction conditions that we previously developed,[12] a trianion **2** would be first generated by deprotonation in the presence of excessive base. An intramolecular oxidative coupling of the enolate with the indole moiety mediated by I_2 will ensue to form a spiroindolenine **3**, which would further cyclize to furnish a polycyclic pyrroloindoline **4** through nucleophilic attack of the resulting imine by nitrogen. Although intramolecular oxidative coupling of dianions had been well studied in our previous reports,[10,12] site selective intramolecular oxidative

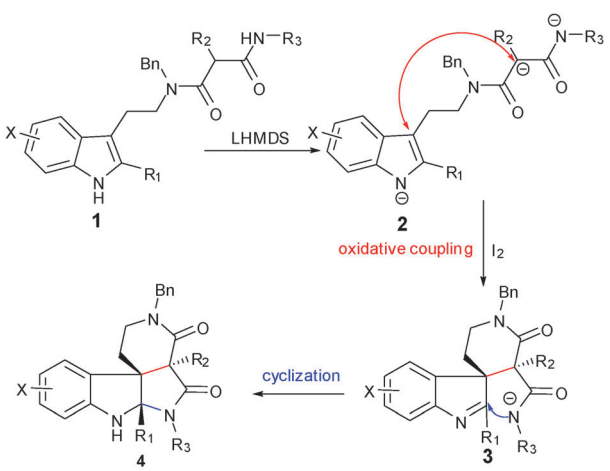
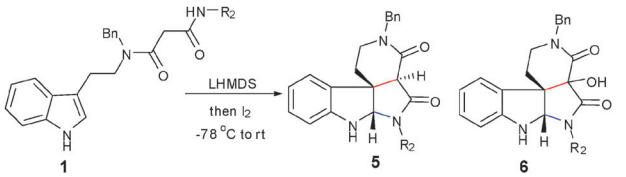


Fig. 1 Oxidative coupling/condensative cyclization of malonic diamides.

[a] *School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China*
[b] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China. E-mail: xiewq@mail.sioc.ac.cn, madw@mail.sioc.ac.cn; Fax: +86-21-64166128; Tel: +86-21-54925341*

† Electronic supplementary information (ESI) available: General experimental procedure and spectra data of starting materials and products. CCDC 879839 and 879840. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc33129b

Table 1 The influence of the protecting group of the amide on the cascade annulation reaction[c]



Entry	Substrate, R_2	Product, yield[a]
1	**1a**, H	**5a**, 21%[b]
2	**1b**, Ph	**6**, 43%
3	**1c**, Bn	**5c**, 59%
4	**1d**, CO_2Me	**5d**, 80%
5	**1e**, Ts	**5e**, 80%

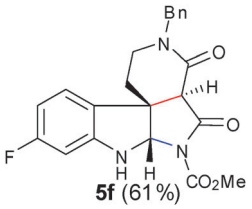
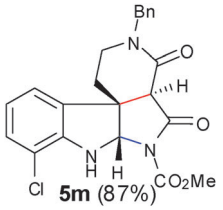
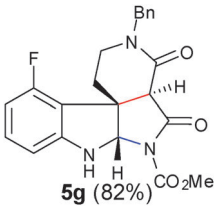
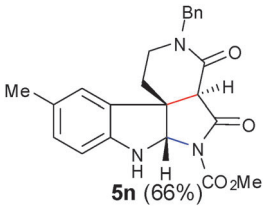
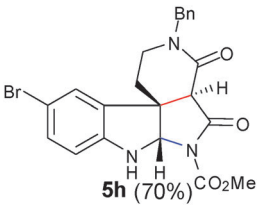
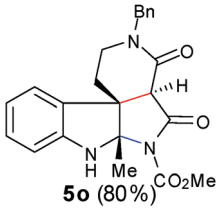
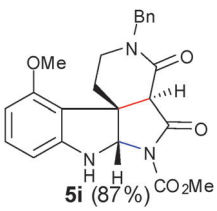
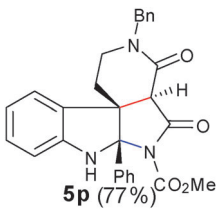
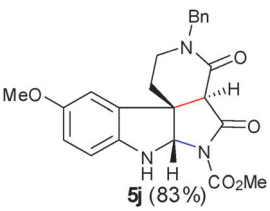
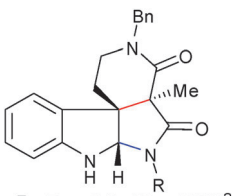
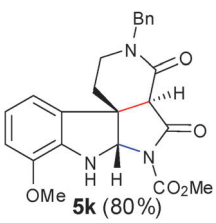
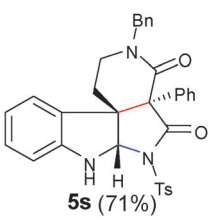
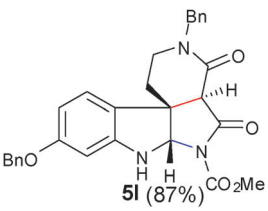
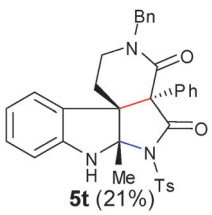
[a] Isolated yield. [b] 30% dimerization product was isolated. [c] General conditions: malonic diamide **1** (1.0 equiv.), LiHMDS (3.3 equiv.), I_2 (1.1 equiv.).

coupling of trianion **2** remained a challenge. With this uncertainty in mind, we initiated our study by applying the previous oxidative coupling conditions[12] to malonic diamide **1** except that one more equivalent of base was employed to ensure the generation of trianion **2**.

Aware that the nucleophilicity of nitrogen was influenced by the attached protecting group, we first began to screen the protecting groups on the appendant amide. As shown in Table 1, a low yield was obtained (21%) when no protecting group was present on nitrogen (Table 1, entry 1). Isolation of the dimerization product of diamide **1a** indicated that the intramolecular oxidative coupling reaction had slowed down, probably due to the decreased acidity of the malonic methylene proton, which was consistent with our previous observations.[10,12] Better results were achieved by using phenyl or benzyl groups as the protecting group (entries 2 and 3). Although no starting material was observed in the reaction mixtures, oxidative coupling products without formation of the second ring were monitored by TLC but were too unstable to be isolated. Interestingly, when the phenyl protected substrate **1b** was subjected to the standard conditions, the oxidative product **6** was produced, presumably *via* air oxidation of the cyclization product. Gratifyingly, the yields were significantly improved when electron-withdrawing groups such as methyl carbamate and tosyl were attached on the nitrogen (entries 4 and 5), which both gave comparable yields. It should be noted that only a single stereoisomer was detected in all the reaction mixtures and the relative configuration of the products was established by crystallographic analysis of **5d**.

Subsequently, we evaluated the substrate scope of the cascade annulation reaction. A series of malonic diamides with various substituents on the indole were synthesized and submitted to the reaction conditions. Gratifyingly, both malonic diamides with electron-donating and withdrawing groups on the indole ring gave the corresponding products in good yields (Table 2, entries 1 to 11), which showed good functional group tolerance of the cascade annulation reaction. Remarkably, substrates embedded with 2-substituted indole also afforded products with contiguous quaternary carbon centers in good yields (entries 10 and 11). We also prepared α-substituted malonic diamides to make contiguous quaternary carbon centers *via* intramolecular oxidative coupling. However, α-methyl malonic diamide with methyl

Table 2 Substrate scope of the cascade annulation reaction[c]

Entry	Product (yield)	Entry	Product (yield)
1	 **5f** (61%)	8	 **5m** (87%)
2	 **5g** (82%)	9	 **5n** (66%)
3	 **5h** (70%)	10	 **5o** (80%)
4	 **5i** (87%)	11	 **5p** (77%)
5	 **5j** (83%)	12	 **5q** R = CO_2Me (0%)[a] **5r** R = Ts, (25%)[b]
6	 **5k** (80%)	13	 **5s** (71%)
7	 **5l** (87%)	14	 **5t** (21%)

[a] 50% starting material was recovered. [b] 7% starting material was recovered. [c] General conditions: malonic diamide **1** (1.0 equiv.), LiHMDS (3.3 equiv.), I_2 (1.1 equiv.).

carbamate on the appendant amide was unreactive under the standard conditions (entry 12, **5q**). A switch of the protecting group to tosyl afforded the annulation product **5r** in only 25% yield. The yield was greatly improved (71%) when a phenyl group was present on the α position of the malonic diamide (entry 13). These results further confirmed that the intramolecular oxidative coupling reaction may be related to the pK_a of the two oxidative coupling partners. Interestingly, when two substituents were present at the same time (2-methyl indole and α-phenyl malonic diamide), three contiguous quaternary carbon centers could be generated albeit in a low yield (21%, entry 14).

In conclusion, a concise and efficient protocol for the construction of polycyclic pyrroloindolines was reported. Starting from malonic diamides embedded with an indole, tetracyclic products were formed in one pot *via* an intramolecular oxidative coupling/condensative cyclization cascade process with moderate to good yields. In this reaction, two rings and at least one quaternary carbon center, in some cases two or three continuous quaternary carbon centers, could be formed, which showed the capability and efficiency of this cascade annulation reaction. Furthermore, the structures of the annulation products highly resembled those of natural products and those compounds could be used as candidates in medicinal chemistry. Application of this method to the total synthesis of natural products and assays of biological activities of polycyclic pyrroloindoline products are currently being pursued in our lab.

Notes and references

1 U. Anthoni, C. Christophersen and P. H. Nielsen, Naturally Occurring Cyclotryptophans and Cyclotryptamines, in *Alkaloids: Chemical & Biological Perspectives*, ed. S. W. Pelletier, Pergamon, Oxford, 1999, vol. 13, pp. 163.

2 For reviews: (*a*) D. Crich and A. Banerjee, *Acc. Chem. Res.*, 2007, **40**, 151; (*b*) A. Steven and L. E. Overman, *Angew. Chem., Int. Ed.*, 2007, **46**, 5488; (*c*) J. Kim and M. Movassaghi, *Chem. Soc. Rev.*, 2009, **38**, 3035; (*d*) P. Ruiz-Sanchis, S. A. Savina, F. Albericio and M. Álvarez, *Chem.–Eur. J.*, 2011, **17**, 1388; selected examples: (*e*) M. Taniguchi and T. Hino, *Tetrahedron*, 1981, **37**, 1487; (*f*) S. P. Marsden, K. M. Depew and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1994, **116**, 11143; (*g*) L. E. Overman, D. V. Paone and B. A. Stearns, *J. Am. Chem. Soc.*, 1999, **121**, 7702; (*h*) J. F. Austin, S. G. Kim, C. J. Sinz, W. J. Xiao and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5482; (*i*) B. M. Trost and J. Quancard, *J. Am. Chem. Soc.*, 2006, **128**, 6314; (*j*) T. Lindel, L. Bräuchle, G. Golz and P. Böhrer, *Org. Lett.*, 2007, **9**, 283; (*k*) J. Kim, J. A. Ashenhurst and M. Movassaghi, *Science*, 2009, **324**, 238; (*l*) T. Newhouse and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 10886; (*m*) V. R. Espejo, X.-B. Li and J. D. Rainier, *J. Am. Chem. Soc.*, 2010, **132**, 8282; (*n*) L. M. Repka, J. Ni and S. E. Reisman, *J. Am. Chem. Soc.*, 2010, **132**, 14418; (*o*) A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw and N. K. Garg, *Tetrahedron*, 2010, **66**, 4687.

3 For selected examples of the total synthesis of physostigmine: (*a*) D. Aburano, T. Yoshida, N. Miyakoshi and C. Mukai, *J. Org. Chem.*, 2007, **72**, 6878; (*b*) M. G. Kulkarni, A. P. Dhondge, A. S. Borhade, D. D. Gaikwad, S. W. Chavhan, Y. B. Shaikh, V. B. Ningdale, M. P. Desai, D. R. Birhade and M. P. Shinde, *Tetrahedron Lett.*, 2009, **50**, 2411; (*c*) P. D. Rege and F. Johnson, *J. Org. Chem.*, 2003, **68**, 6133; (*d*) J. P. Marino, S. Bogdan and K. Kimura, *J. Am. Chem. Soc.*, 1992, **114**, 5566; (*e*) T. Matsuura, L. E. Overman and D. J. Poon, *J. Am. Chem. Soc.*, 1998, **120**, 6500; (*f*) A. S. ElAzab, T. Taniguchi and K. Ogasawara, *Org. Lett.*, 2000, **2**, 2757; (*g*) S. Takano, E. Goto, M. Hirama and K. Ogasawara, *Chem. Pharm. Bull.*, 1982, **30**, 2641.

4 For the total synthesis of minfiesine: (*a*) A. B. Dounay, L. E. Overman and A. D. Wrobleski, *J. Am. Chem. Soc.*, 2005, **127**, 10186; (*b*) A. B. Dounay, P. G. Humphreys, L. E. Overman and A. D. Wrobleski, *J. Am. Chem. Soc.*, 2008, **130**, 5368; (*c*) L. Shen, M. Zhang, Y. Wu and Y. Qin, *Angew. Chem., Int. Ed.*, 2008, **47**, 3618; (*d*) S. B. Jones, B. Simmons and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 13606; (*e*) G. Li and A. Padwa, *Org. Lett.*, 2011, **13**, 3767; (*f*) P. Liu, J. Wang, J. Zhang and F. G. Qiu, *Org. Lett.*, 2011, **13**, 6426.

5 (*a*) K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 3224; (*b*) J. W. H. Li and J. C. Vederas, *Science*, 2009, **325**, 161; (*c*) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, *Nat. Chem.*, 2010, **2**, 735; for a copper-catalyzed oxidative process to spiroindolines: (*d*) L. El Kaïm, L. Grimaud, X. Le Goff, M. Menes-Arzate and L. D. Miranda, *Chem. Commun.*, 2011, **47**, 8145.

6 Selected examples for oxidative homocoupling: (*a*) D. Ivanoff and A. Spassoff, *Bull. Soc. Chim. Fr.*, 1935, **2**, 76; (*b*) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, 1971, **93**, 4605; (*c*) T. J. Brocksom, N. Petragnani, R. Rodrigues and H. La Scala Teixeira, *Synthesis*, 1975, 396; (*d*) R. H. Frazier and R. L. Harlow, *J. Org. Chem.*, 1980, **45**, 5408; (*e*) J. L. Belletire and D. J. Fry, *J. Org. Chem.*, 1987, **52**, 2549; (*f*) P. Renaud and M. A. Fox, *J. Org. Chem.*, 1988, **53**, 3745; (*g*) R. Quermann, R. Maletz and H. J. Schafer, *Liebigs Ann. Chem.*, 1993, **11**, 1219; (*h*) N. Kise, K. Tokioka and Y. Aoyama, *J. Org. Chem.*, 1995, **60**, 1100; (*i*) T. Langer, M. Illich and G. Felmchen, *Tetrahedron Lett.*, 1995, **36**, 4409; (*j*) J. W. Kim, J. J. Lee, S. H. Lee and K. H. Ahn, *Synth. Commun.*, 1998, **28**, 1287.

7 Selected examples for oxidative heterocoupling: (*a*) Y. Ito, T. Konoike, T. Harada and T. Saegusa, *J. Am. Chem. Soc.*, 1977, **99**, 1487; (*b*) P. S. Baran, J. M. Richter and D. W. Lin, *Angew. Chem., Int. Ed.*, 2005, **44**, 609; (*c*) P. S. Baran and M. P. DeMartino, *Angew. Chem., Int. Ed.*, 2006, **45**, 7083; (*d*) J. M. Richter, B. Whitefield, T. J. Maimone, D. W. Lin, P. Castroviejo and P. S. Baran, *J. Am. Chem. Soc.*, 2007, **129**, 12857; (*e*) J. M. Richter, B. Whitefield, T. J. Maimone, D. W. Lin, P. Castroviejo and P. S. Baran, *J. Am. Chem. Soc.*, 2007, **129**, 12857; (*f*) M. P. DeMartino, K. Chen and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 11546.

8 (*a*) P. S. Baran and J. M. Richter, *J. Am. Chem. Soc.*, 2004, **126**, 7450; (*b*) P. S. Baran and J. M. Richter, *J. Am. Chem. Soc.*, 2005, **127**, 15394; (*c*) P. S. Baran, T. J. Maimone and J. M. Richter, *Nature*, 2007, **446**, 404; (*d*) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 17938.

9 (*a*) C. L Martin, L. E. Overman and J. M. Rohde, *J. Am. Chem. Soc.*, 2010, **132**, 4894; (*b*) C. L Martin, L. E. Overman and J. M. Rohde, *J. Am. Chem. Soc.*, 2008, **130**, 7568.

10 (*a*) Z. Zuo, W. Xie and D. Ma, *J. Am. Chem. Soc.*, 2010, **132**, 13226; (*b*) Z. Zuo and D. Ma, *Angew. Chem., Int. Ed.*, 2011, **50**, 12008.

11 (*a*) E. S. Krygowski, K. Murphy-Benenato and M. D. Shair, *Angew. Chem., Int. Ed.*, 2008, **47**, 1680; (*b*) H. G. Lee, J. Y. Ahn, A. S. Lee and M. D. Shair, *Chem.–Eur. J.*, 2010, **16**, 13058; (*c*) S. B. Herzon, L. Lu, C. M. Woo and S. L. Gholap, *J. Am. Chem. Soc.*, 2011, **133**, 7260.

12 F. Fan, W. Xie and D. Ma, *Org. Lett.*, 2012, **14**, 1405.