ORGANIC LETTERS

2013
Vol. 15, No. 14
3578–3581

Highly Efficient Synthesis of Mixed 3,3′-Bisindoles via Rh(II)-Catalyzed Three-Component Reaction of 3-Diazooxindoles with Indoles and Ethyl Glyoxylate

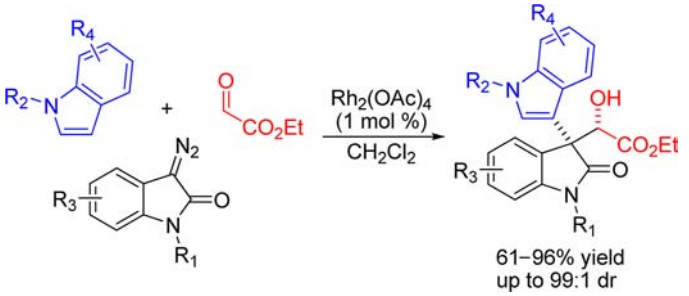
Dong Xing,* Changcheng Jing, Xinfeng Li, Huang Qiu, and Wenhao Hu*

Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, 3663 North Zhongshan Road, Shanghai, 200062, China

dxing@sat.ecnu.edu.cn; whu@chem.ecnu.edu.cn

Received May 19, 2013

ABSTRACT



A series of mixed 3,3′-bisindoles were efficiently synthesized via a $Rh_2(OAc)_4$-catalyzed three-component reaction of 3-diazooxindoles with indoles and ethyl glyoxylate in high yields with excellent diastereoselectivities. The product easily underwent further synthetic transformations and could be potentially applied to the total synthesis of (±)-gliocladin C and related natural alkaloids.

3-(2-Hydroxy-alkyl)-3-indol-3′-yloxindoles (**A**, Figure 1) belong to a unique family of mixed 3,3′-bisindoles that display various biological activities.[1] They have been used as key intermediates for the total synthesis of (+)-gliocladin C[2,3] and could be potentially applied to the total synthesis of a number of other indole alkaloids possessing 3,3′-bisindole skeletons (Figure 1).[4−8] Therefore, much effort has been focused toward methodological development for the synthesis of such molecules as well as their further applications to the total synthesis of related natural products.[2,3,4b,7,9] The Overman research group has developed an elegant Mukaiyama−aldol reaction of 2-siloxyindole with aldehydes,[10] which was successfully applied to the total synthesis of (+)-gliocladin C.[2] Trost and co-workers have reported an efficient protocol by Pd(0)-catalyzed

(1) (a) Bindra, J. S. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: 1973; Vol. 14, p 84. (b) Cordell, G. A.; Saxton, J. E. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: 1981; Vol. 20, p 3. (c) Kobayashi, M.; Aoki, S.; Gato, K.; Matsunami, K.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2449. (d) Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: 1999; Vol. 13, p 163.

(2) Overman, L. E.; Shin, Y. *Org. Lett.* **2007**, *9*, 339.

(3) Song, J.; Guo, C.; Adele, A.; Yin, H.; Gong, L.-Z. *Chem.—Eur. J.* **2013**, *19*, 3319.

(4) For reviews, see: (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (b) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (c) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem.—Eur. J.* **2011**, *17*, 1388. (d) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.

(5) (a) DeLorbe, J. E.; Jabri, S. Y.; Mennen, S. M.; Overman, L. E.; Zhang, F.-L. *J. Am. Chem. Soc.* **2011**, *133*, 6549. (b) DeLorbe, J. E.; Horne, D.; Jove, R.; Mennen, S. M.; Nam, S.; Zhang, F.-L.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 4117.

(6) (a) Boyer, N.; Movassaghi, M. *Chem. Sci.* **2012**, *3*, 1798. (b) Boyer, N.; Morrison, K. C.; Kim, J.; Hergenrother, P. J.; Movassaghi, M. *Chem. Sci.* **2013**, *4*, 1646.

(7) Trost, B. M.; Xie, J.; Sieber, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 20611.

(8) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655.

(9) Arai, T.; Yamamoto, Y.; Awata, A.; Kamiya, K.; Ishibashi, M.; Arai, M. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2486.

(10) Adhikari, S.; Caille, S.; Hanbauer, M.; Ngo, V. X.; Overman, L. E. *Org. Lett.* **2005**, *7*, 2795.

10.1021/ol401414w
Published on Web 06/28/2013

hydrocarbonation of allenes with 3-aryl-3′-yloxindoles that can be used to synthesize mixed 3,3′-bisindoles.[7] Gong and co-workers reported a convenient method for the α-alkylation of aldehydes with 3-hydroxy-3-indol-3′-yloxindole and furnished the total synthesis of (+)-gliocladin C.[3] A similar α-alkylation strategy of cyclic ketones has also been developed by Guo, Peng and co-workers.[11] Despite their high synthetic values, however, all of those methods required the indole ring and the oxindole moiety to be preconnected at the C3 and C3′ positions before the 2-hydroxy-substituted side chain was further introduced. Therefore, it would be highly efficient if one could assemble the three parts in one single step to provide the desired 3-(2-hydroxy-alkyl)-3-indol-3′-yloxindole product. Toward this end, herein we report an efficient and straightforward three-component reaction for the synthesis of such molecules starting from 3-diazooxindoles with indoles and ethyl glyoxylate as catalyzed by $Rh_2(OAc)_4$ (Scheme 1, path 2).

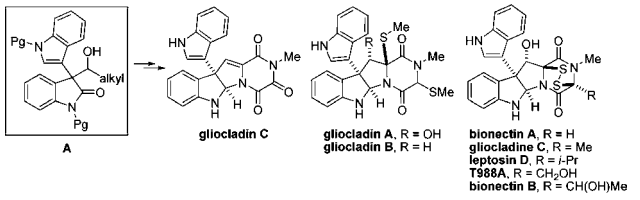
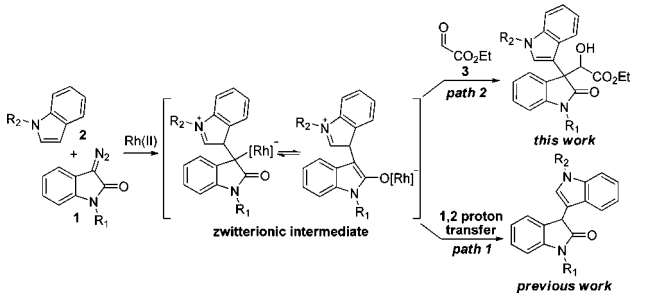


Figure 1. 3-(2-Hydroxy-alkyl)-3-indol-3′-yloxindole (**A**) as key intermediates for the synthesis of a number of natural alkaloids.

As part of our continuous interest in exploring new multicomponent reactions (MCRs) based on the electrophilic trapping of active intermediates generated from metal carbenoids,[12,13] we have recently developed an efficient three-component reaction in which an active zwitterionic intermediate generated from an aryl diazoester and indole was efficiently trapped by imine to afford 3-substituted indole moieties.[14] In view of its high efficiency, we decided to apply this novel zwitterionic-trapping process to synthesize mixed 3,3′-bisindoles by choosing 3-diazooxindole as the diazo source[15] with indole and a suitable electrophile (Scheme 1, path 2). However, due to the relatively low reactivity of 3-diazooxindole[16] and the rapid 1,2-proton transfer process for the zwitterionic intermediate to afford C−H insertion products, which itself had been used as an elegant approach for the synthesis of 3-indol-3′-yloxindole (Scheme 1, path 1),[7,17] it is not clear whether the zwitterionic intermediate could be efficiently trapped by a corresponding electrophile. As such, the key point for the desired three-component reaction would be the choice of an efficient electrophile.

Scheme 1. Trapping of Zwitterionic Intermediate with Ethyl Glyoxylate for Three-Component Reactions



As the starting point, ethyl glyoxylate (**3**) was chosen for its high electrophilicity[18] as well as the easy-functionalizing feature of the ester group resulting in the desired product. Therefore, benzyl-substituted 3-diazooxindole (**1a**) and benzyl-substituted indole (**2a**) were allowed to react with ethyl glyoxylate (**3**) in CH_2Cl_2 in the presence of 1 mol % $Rh_2(OAc)_4$ and 4 Å molecular sieves. To our great delight, the desired three-component product **4a** *via* a zwitterion generation/Aldol addition sequence was obtained in very good yield (94%) and diastereoselectivity (94:6) (Table 1, entry 1). It is worth mentioning that when ethyl glyoxylate **3** was directly subjected to the C−H insertion product 1,1′-dibenzyl-3-indol-3′-yloxindole, **4a** was not obtained either with or without $Rh_2(OAc)_4$,[19,20] indicating the significance and efficiency of this three-component zwitterionic-trapping process. With the initial result, further condition

(11) Song, L.; Guo, Q.-X.; Li, X.-C.; Tian, J.; Peng, Y.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 1899.

(12) For recent leading reviews on carbenoid chemistry, see: (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (c) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (d) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577. (e) Zhu, S.-F.; Zhou, Q.-L. *Acc. Chem. Res.* **2012**, *45*, 1365. (f) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162.

(13) For selected examples, see: (a) Hu, W. H.; Xu, X. F.; Zhou, J.; Liu, W. J.; Huang, H. X.; Hu, J.; Yang, L. P.; Gong, L. Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (b) Zhang, X.; Huang, H.; Guo, X.; Guan, X.; Yang, L.; Hu, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 6647. (c) Guan, X. Y.; Yang, L. P.; Hu, W. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2190. (d) Jiang, J.; Xu, H.-D.; Xi, J.-B.; Ren, B.-Y.; Lv, F.-P.; Guo, X.; Jiang, L.-Q.; Zhang, Z.-Y.; Hu, W.-H. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (e) Zhou, C.-Y.; Wang, J.-C.; Wei, J.; Xu, Z.-J.; Guo, Z.; Low, K.-H.; Che, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11376. (f) Li, M.; Zan, L.; Prajapati, D.; Hu, W. *Org. Biomol. Chem.* **2012**, *10*, 8808. (g) Ren, L.; Lian, X.-L.; Gong, L.-Z. *Chem.— Eur. J.* **2013**, *19*, 3315.

(14) Qiu, H.; Li, M.; Jiang, L.-Q.; Lv, F.-P.; Zan, L.; Zhai, C.-W.; Doyle, M. P.; Hu, W.-H. *Nat. Chem.* **2012**, *4*, 733.

(15) For recent examples of 3-diazooxindole-involved three-component reactions via electrophilic trapping of either oxonium or ammonium ylides, see: Alcaide, B.; Almendros, P.; Aragoncillo, C.; Callejo, R.; Ruiz, M. P.; Torres, M. R. *Eur. J. Org. Chem.* **2012**, *2012*, 2359 and ref 12g.

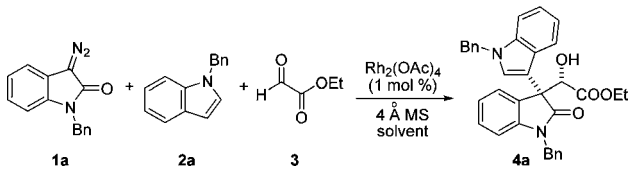
(16) For limited examples of cyclopropanations of 3-diazooxindoles, see: (a) Muthusamy, S.; Gunanathan, C. *Synlett* **2003**, 1599. (b) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505. (c) Reddy, B. V. S.; Rajasekaran, T.; Karthik, G.; Rao, T. P. *Tetrahedron Lett.* **2012**, *53*, 3416. (d) Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. *Org. Lett.* **2012**, *15*, 42. (e) Awata, A.; Arai, T. *Synlett* **2013**, 29. (f) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197.

(17) Muthusamy, S.; Gunanathan, C.; Babu, S. A.; Suresh, E.; Dastidar, P. *Chem. Commun.* **2002**, 824.

(18) (a) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (b) Pousse, G.; Cavelier, F. L.; Humphreys, L.; Rouden, J.; Blanchet, J. R. M. *Org. Lett.* **2010**, *12*, 3582. (c) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Gianelli, C.; Mancinelli, M.; Bartoli, G.; Bencivenni, G. *Adv. Synth. Catal.* **2011**, *353*, 2953. (d) Zhao, J.-F.; Tan, B.-H.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 349.

(19) For details, see the Supporting Information.

Table 1. Reaction Condition Optimization[a]



1a 2a 3 4a

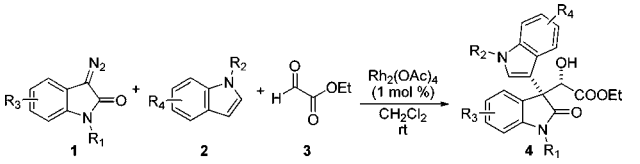
entry	solvent	temp (°C)	yield (%)[b]	dr[c]
1	CH_2Cl_2	25	94	94:6
2	DCE	25	94	94:6
3	THF	25	<5	–
4	toluene	25	93	85:15
5	CH_2Cl_2	40	76	95:5
6[d]	CH_2Cl_2	25	88	97:3

[a] Reaction conditions: To the mixture of **2a** (0.11 mmol), **3** (0.2 mmol), 4 Å MS (100 mg), and 1 mol % $Rh_2(OAc)_4$ in 0.5 mL of the solvent was added **1a** (0.1 mmol) in 0.5 mL of the solvent *via* syringe pump over 30 min. [b] Isolated yield. [c] Determined by HPLC. [d] Without the addition of 4 Å MS.

optimizations were conducted. A brief solvent screening revealed that this three-component reaction ran smoothly in 1,2-dichloroethane (DCE) and toluene but did not afford the desired product in tetrahydrofuran (THF); however, with toluene as the solvent, relatively poor diastereoselectivity was achieved (Table 1, entries 2–4). Raising the reaction temperature to 40 °C resulted in a decreased yield (Table 1, entry 5). When the reaction was conducted without 4 Å molecular sieves, the desired product was obtained in even higher diastereoselectivity (97:3) while the yield remained satisfactory (88%) (Table 1, entry 6).

To test the substrate generality of this Rh(II)-catalyzed three-component reaction, a series of substituted 3-diazooxindoles and indoles were first investigated under the optimized reaction conditions. Different protecting groups on the nitrogen atom of 3-diazooxindole including benzyl (**1a**), Cbz (**2a**), and Boc (**3a**) proved to be efficient in providing corresponding three-component products in high yields with excellent diastereoselectivities (Table 2, entries 1–3). On the other hand, alkyl substituents such as a methyl or benzyl group on the nitrogen atom of the indole component also provided the desired three-component products (Table 2, entries 1, 4). Substituents at the 5- or 6-position of the aromatic ring of 3-diazooxindole were evaluated: chloro-substituted substrates gave lower yields but with excellent diastereoselectivities, and 5-methyl-substituted 3-diazooxindole gave the corresponding product in high yield and excellent diastereoselectivity (Table 2, entries 5–7). A more thorough substituting effect on the indole ring was also investigated. While different substituents on the 5-, 6-, and 7-position of the indole ring provided corresponding products in moderate to good yields with excellent diastereoselectivities, a substituent at the 4-position gave the desired product in poor yield, indicating a strong steric effect (Table 2, entries 8–13). The relative stereochemistry of products was assigned in analogy with **4k** as determined by single-crystal X-ray diffraction (Figure 2). The use of other aldehydes, such as benzaldehyde or cinnamaldehyde, as the substrate resulted in no desired product formation under current reaction conditions, indicating the high electrophilicity of ethyl glyoxylate was essential for this three-component reaction to occur. The broad scope of this three-component reaction allows us to utilize this methodology for the rapid synthesis of a series of mixed 3,3′-bisindoles for biological evaluations of their intriguing biologically active features.

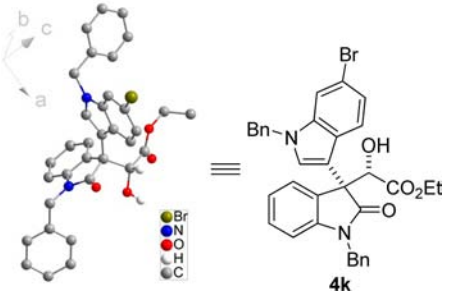
Table 2. Substrate Scope[a]



1 2 3 4

entry	R_1	R_2	R_3	R_4	4	yield (%)[b]	dr[c]
1	Bn	Bn	H	H	**4a**	88	98:2
2	Cbz	Bn	H	H	**4b**	85	95:5
3	Boc	Bn	H	H	**4c**	80	95:5
4	Bn	Me	H	H	**4d**	96	97:3
5	Bn	Bn	5-Cl	H	**4e**	77	99:1
6	Bn	Bn	5-Me	H	**4f**	92	99:1
7	Bn	Bn	6-Cl	H	**4g**	61	94:6
8	Bn	Bn	H	5-Br	**4h**	67	99:1
9	Bn	Bn	H	5-NO_2	**4i**	79	97:3
10	Bn	Bn	H	5-MeO	**4j**	96	98:2
11	Bn	Bn	H	6-Br	**4k**	86	97:3
12	Bn	Bn	H	7-Me	**4l**	67	97:3
13	Bn	Bn	H	4-Br	**4m**	22	98:2

[a] Reaction conditions: To the mixture of **2** (0.33 mmol), **3** (0.6 mmol), and 1 mol % $Rh_2(OAc)_4$ in 1.5 mL CH_2Cl_2 was added **1** (0.3 mmol) in 1.5 mL of CH_2Cl_2 *via* syringe pump over 30 min. [b] Isolated yield. [c] Determined by HPLC.



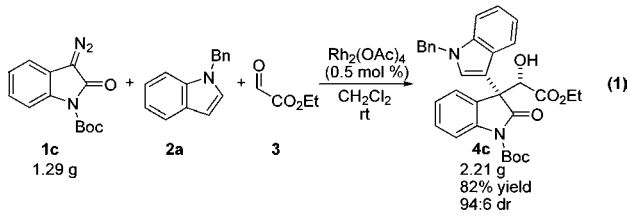
4k

Figure 2. X-ray crystal structure of **4k**.

To demonstrate the synthetic potential of this new three-component reaction, we explored a gram scale reaction of

(20) Direct Aldol-type addition of ethyl glyoxylate to 3-alkyl or 3-phenyl substituted 2-oxindole catalyzed by cinchona alkaloids has been reported; see: Pesciaioli, F.; Righi, P.; Mazzanti, A.; Gianelli, C.; Mancinelli, M.; Bartoli, G.; Bencivenni, G. *Adv. Synth. Catal.* **2011**, *353*, 2953.

N-Boc-3-diazooxindole (**1c**) with *N*-Bn-indole (**2a**) and ethyl glyoxylate (**3**). As shown in eq 1, the use of only 0.5 mol % $Rh_2(OAc)_4$ promoted the formation of **4c** in 82% yield with 94:6 diastereoselectivity (eq 1).



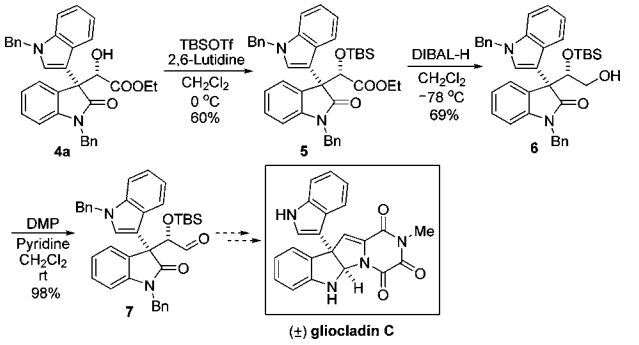
(1)

Due to the intriguing 3,3′-bisindole structural feature established through this method, we sought to explore its further synthetic applications toward the synthesis of related natural alkaloids. The hydroxyl group of **4a** was first protected with the TBS group to afford **5** in good yield. Reduction of the ester group of **5** with DIBAL-H furnished the corresponding primary alcohol in 69% yield. Then, under Dess-Martin conditions, primary alcohol **6** was oxidized into aldehyde **7**, which could be used as a key intermediate for the total synthesis of (±)-gliocladin C (Scheme 2).[7]

In summary, we have developed a highly efficient $Rh_2(OAc)_4$-catalyzed three-component reaction of 3-diazooxindoles with indoles and ethyl glyoxylate. This reaction allows the step economical formation of mixed 3,3′-bisindoles bearing a quaternary carbon center in high yields with excellent diastereoselectivities. The product easily undergoes further synthetic elaborations to obtain key intermediates that could be potentially applied to the total synthesis of natural alkaloid (±)-gliocladin C. A catalytic asymmetric version of this three-component reaction[21] and further application to the synthesis of related natural alkaloids bearing 3,3′-bisindole structural motifs are currently being investigated in our laboratory.

(21) For a recently reported example of asymmetric trapping of an ammonium ylide intermediate with ethyl glyoxylate as catalyzed by a $Rh_2(OAc)_4$/chiral phosphoric acid cooperative system, see: ref 13g.

Scheme 2. Synthetic Applications of Product **4a**



Acknowledgment. W.H. thanks NSF of China (20932003 and 21125209), the MOST of China (2011CB808600), and STCSM (12JC1403800) for financial support. D.X. thanks the Fundamental Research Funds for the Central Universities (FRFCU) from East China Normal University. We thank Prof. R. Y. Wang from Xian Jiaotong-Liverpool University for X-ray crystallographic structure determination.

Supporting Information Available. Typical experimental procedure and characterization for all products, X-ray data of **4k** in CIF format (CCDC: 940495). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.