

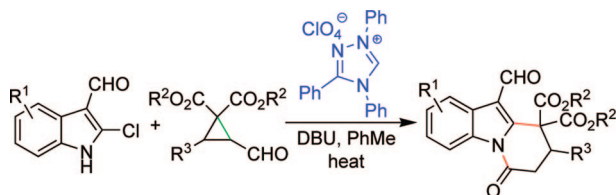
N-Heterocyclic Carbene-Catalyzed Domino Ring-Opening/Redox Amidation/Cyclization Reactions of Formylcyclopropane 1,1-Diesters: Direct Construction of a 6–5–6 Tricyclic Hydropyrido[1,2-*a*]indole Skeleton

Ding Du, Linxia Li, and Zhongwen Wang*

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, 30071, People's Republic of China

wzwrj@nankai.edu.cn

Received March 27, 2009



Catalyzed by N-heterocyclic carbenes (NHCs), domino ring-opening/redox amidation/cyclization reactions of the readily available formylcyclopropane 1,1-diesters with 2-chloro-1H-indole-3-carbaldehydes were reported. This methodology provides an efficient and direct construction of a 6–5–6 tricyclic hydropyrido[1,2-*a*]indole skeleton, which can be potentially applied for the synthesis of several types of polycyclic indole alkaloids.

Hydropyrido[1,2-*a*]indole is a 6–5–6 tricyclic core skeleton existing in a large class of naturally bioactive polycyclic indole alkaloids (Figure 1).¹ Great efforts to construct such skeleton have been documented, and most of the typical strategies started from the indole skeleton, and the additional piperidine ring was built through transition-metal-catalyzed C–C bond formation,² intra/intermolecular condensations,³ radical cyclizations,⁴ nu-

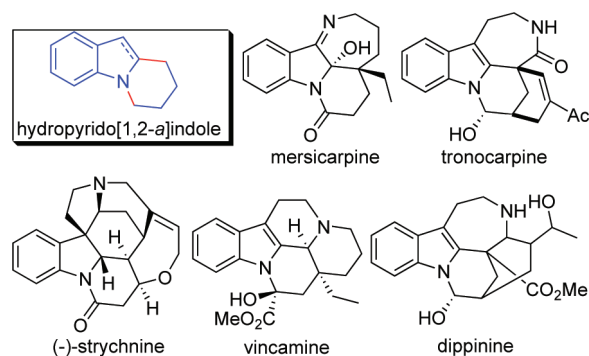


FIGURE 1. Selected typical alkaloids with a hydropyrido[1,2-*a*]indole skeleton.

cleophilic substitutions,⁵ acid-induced cyclizations,⁶ cycloadditions,⁷ and Pauson–Khand reactions.⁸ These strategies usually need multiple steps to construct the additional piperidine skeleton. Thus, the discovery of new, general, and direct methods for the construction of such skeleton remains a formidable challenge in pursuit of efficient and sustainable chemical processes.

Domino reactions⁹ are one of the most important methods for HECCS (highly efficient construction of complex skeleton) in contemporary organic synthesis. As versatile building blocks in modern organic syntheses, activated cyclopropanes have attracted much interest in the field of nucleophilic ring-opening domino reactions.¹⁰ In the research of novel carbon–carbon and carbon–heteroatom bond-forming reactions, N-heterocyclic

(3) For some selected examples, please see: (a) Lotter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. A.; van Otterlo, W. A. L.; de Koning, C. B. *Tetrahedron* **2007**, *63*, 2263. (b) Khodour, O.; Ouyang, A.; Skibo, E. B. *J. Org. Chem.* **2006**, *71*, 5855. (c) Taga, M.; Ohtsuka, H.; Inoue, I.; Kawaguchi, T.; Nomura, S.; Yamada, K.; Date, T.; Hiramatsu, H.; Sato, Y. *Heterocycles* **1996**, *42*, 251. (d) Knight, S. D.; Overman, L. E.; Paireudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776. (e) Kato, M.; Ito, K.; Nishino, S.; Yamakuni, H.; Takasugi, H. *Chem. Pharm. Bull.* **1994**, *42*, 2546.

(4) Selected articles include: (a) Magolan, J.; Carson, C. A.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 1437. (b) Bowman, W. R.; Fletcher, A. J.; Pedersen, J. M.; Lovell, P. J.; Elsegood, M. R. J.; Hernandez Lopez, E.; McKee, V.; Potts, G. B. *Tetrahedron* **2007**, *63*, 191. (c) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561. (d) Menes-Arzate, M.; Martnez, R.; Cruz-Almanza, R.; Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem.* **2004**, *69*, 4001. (e) Tsoinias, A.; Panoussopoulou, M.; Sivananthan, S.; Sugden, D. *Il Farmaco* **2001**, *56*, 725. (f) Caddick, S.; Shering, C. L.; Wadman, S. N. *Tetrahedron* **2000**, *56*, 465. (g) Fiumana, A.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 4209.

(5) Selected articles include: (a) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157. (b) Tanino, H.; Fukushii, K.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004**, *60*, 3273.

(6) (a) Tanaka, M.; Sagawa, S.; Hoshi, J.; Shimoma, F.; Yasue, K.; Ubukata, M.; Ikemoto, T.; Hase, Y.; Takahashi, M.; Sasase, T.; Ueda, N.; Matsushita, M.; Inaba, T. *Bioorg. Med. Chem.* **2006**, *14*, 5781. (b) Bannasar, M.-L.; Zulaica, E.; Alonso, Y.; Vidal, B.; Vazquez, J. T.; Bosch, J. *Tetrahedron: Asymmetry* **2002**, *13*, 95.

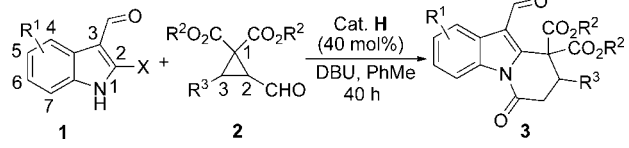
(7) (a) Haider, N.; Kaferbock, J. *Tetrahedron* **2004**, *60*, 6495. (b) Gharagozloo, P.; Lazareno, S.; Miyauchi, M.; Popham, A.; Birdsall, N. J. M. *J. Med. Chem.* **2002**, *45*, 1259. (c) Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261. (d) Eichberg, M. J.; Dorta, R. L.; Lamotte, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479. (e) Beccalli, E. M.; Brogini, G.; La Rosa, C.; Passarella, D.; Pilati, T.; Terraneo, A.; Zecchi, G. *J. Org. Chem.* **2000**, *65*, 8924.

(8) Prez-Serrano, L.; Domnguez, G.; Prez-Castells, J. *J. Org. Chem.* **2004**, *69*, 5413.

(9) Some reviews include: (a) Tieze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. (d) Nicolau, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (e) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619. (f) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143.

(1) Selected references include: (a) Kam, T.-S.; Sim, K.-M.; Pang, H.-S.; Koyano, T.; Hayashi, M.; Komiyama, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4487. (b) Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995. (c) Kam, T.-S.; Sim, K.-M.; Lim, T.-M. *Tetrahedron Lett.* **2000**, *41*, 2733. (d) van Beek, T. A.; Verpoorte, R.; Baerheim Svendsen, A. *Tetrahedron* **1984**, *40*, 737. (e) Ohmoto, T.; Koike, K. *The Alkaloids*; Academic Press: New York, 1989; Vol. 36, pp 135–170. (f) Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455. (g) Pilarcik, T.; Havlicek, J.; Hajicek, J. *Tetrahedron Lett.* **2005**, *46*, 7909, references cited therein.

(2) Some selected examples include: (a) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 346. (b) Liu, J.; Shen, M.; Zhang, Y.; Li, G.; Khodabocus, A.; Rodriguez, S.; Qu, B.; Farina, V.; Senanayake, C. H.; Lu, B. Z. *Org. Lett.* **2006**, *8*, 3573. (c) Jafarpour, F.; Lautens, M. *Org. Lett.* **2006**, *8*, 3601. (d) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (e) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (f) Siebeneicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3042. (g) Nakanishi, M.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1934. (h) Faust, R.; Garratt, P. J.; Jones, R.; Yeh, L.-K. *J. Med. Chem.* **2000**, *43*, 1050.

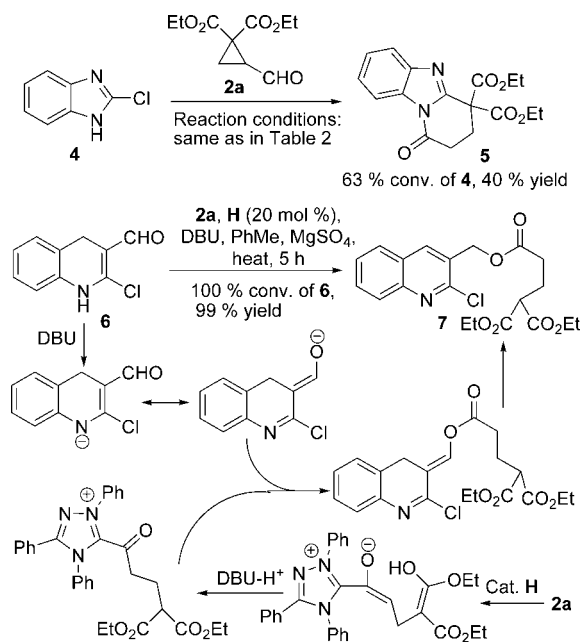
TABLE 2. Investigation of the Reaction Scope^a


entry	1	R ¹	2	R ²	R ³	conv of 1 (%) ^b	yield of 3 (%) ^c
1	1a	H	2a	Et	H	85	3a, 60
2	1e	5-Cl	2a	Et	H	75	3d, 41
3	1f	5-Br	2a	Et	H	78	3e, 52
4	1g	5-I	2a	Et	H	72	3f, 50
5	1h	6-Cl	2a	Et	H	53	3g, 33
6	1i	5-Me	2a	Et	H	>90	3h, 70
7	1j	5-Et	2a	Et	H	88	3i, 76
8	1k	5- <i>i</i> -Pr	2a	Et	H	81	3j, 72
9	1l	5-OMe	2a	Et	H	>90	3k, 74
10	1m	7-Me	2a	Et	H	56	NR
11	1n	4,6-Me ₂	2a	Et	H	59	3l, 37
12	1j	5-Et	2b	Me	H	80	3m, 58
13	1a	H	2b	Me	H	68	3n, 50
14	1j	5-Et	2c	<i>i</i> -Pr	H	59	3o, 40
15	1j	5-Et	2d	Et	Me	60	3p, 36
16	1j	5-Et	2e	Et	Ph	<30	NR

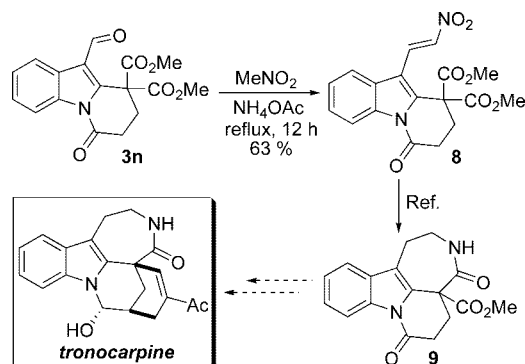
^a Reaction conditions: 1.0 equiv of **1**, 3.0 equiv of **2**, 40 mol % of cat **H**, and 2.0 equiv of DBU, anhydrous MgSO₄, PhMe, 60–70 °C, 40 h, N₂ atmosphere. ^b Determined by recovered **1**. ^c Isolated yields based on **1**.

Substituents on the phenyl ring of substrate **1** significantly affected the yields as well as the conversions. Substrates **1** substituted with electron-withdrawing groups at the 5-position (Table 2, entries 2–4) reacted with **2a** in low to moderate yields and conversions, while substrates **1** with electron-donating groups at the 5-position resulted in good yields and conversions (Table 2, entries 6–9). Substrates **1h** and **1n** with substituents at the 6-position both gave unexplainable decreased yields and conversions (Table 2, entries 5 and 11). The reaction between **1m** and **2a** afforded no desired product, which was probably due to the steric effect of the methyl group at the 7-position (Table 2, entry 10). Several substrates **2** were also examined. Compared to those of **2a**, reactions of **2b** were less effective because of its high volatility (Table 2, entries 12 and 13). The reaction of more sterically hindered **2c** resulted in decreased yield (Table 2, entry 14). While substrate **2d** with methyl substituted at the 3-position gave the desired product **3p**, substrate **2e** with phenyl substituted at the 3-position did not work (Table 2, entries 15 and 16).

The reaction of 2-chloro-1*H*-benzimidazole **4** with **2a** was also found to be applicable to the synthesis of imidazole-fused piperidone **5**, although in 63% conversion and 40% yield (Scheme 2). Several other heteroaromatic compounds have also been tested. 2,4,5-Tribromo-1*H*-imidazole decomposed quickly under the reaction condition without desired product. The reaction of 5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde was very complex. It was interesting that, instead of undergoing redox amidation, the reaction of 2-chloro-1,4-dihydroquinoline-3-carbaldehyde **6** with **2a** gave redox esterification product **7** in quantitative yield, the mechanism of which was probably via a domino ring-opening/esterification/ aromatization process (Scheme 2).

SCHEME 2. Reactions of 2-Chloro-1*H*-benzimidazole **4** and 2-Chloro-1,4-dihydroquinoline-3-carbaldehyde **6** with **2a**

SCHEME 3. Potential Application to the Synthesis of a Tronocarpine Substructure



The potential application of this method is illuminated by the synthesis of the tetracyclic subunit of tronocarpine (Scheme 3). Product **3n** obtained from **1a** and **2b** was treated with MeNO₂ to give nitroalkene **8** (63% yield), which could be transformed into **9** by the reported method.¹⁵ Tetracyclic product **9** contains four of the five rings of tronocarpine as well as suitable functionality for potential conversion to this natural product.

In conclusion, we have demonstrated a novel domino ring-opening/redox amidation/cyclization reaction between 2-chloro-1*H*-indole-3-carbaldehydes and the readily available FCP 1,1-diester. This methodology provides an efficient and direct access to a 6–5–6 tricyclic hydroxyindole skeleton. Additionally, the application of this method to synthesize the tetracyclic core skeleton of the natural product tronocarpine has also been illustrated. Further investigation of the reaction scope is currently underway.

Experimental Section

General Procedure for the Synthesis of 3: To an oven-dried 50 mL three-necked glassware were charged 150 mg of anhydrous

(13) Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949.

(14) See Supporting Information, and CCDC-719430 (**3a**) contains 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) The synthesis of compound **9** from **8** has been accomplished: Mahboobi, V. S.; Burgemeister, T.; Kastner, F. *Arch. Pharm.* **1995**, 328, 29.

MgSO₄ and 56 mg (0.14 mmol) of catalyst **H**. 2-Chloro-1*H*-indole-3-carbaldehydes **1** (0.35 mmol), 2-formylcyclopropane-1,1-dicarboxylates **2** (1.05 mmol), 8 mL of dry toluene, and 105 μ L (0.70 mmol) of DBU were then added sequentially under a positive pressure of nitrogen. The reaction mixture was heated to 60–70 °C for 40 h. The mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by silica gel chromatography to afford products **3** and recovered materials **1**.

3a: 85% conv, 60% yield; white solid, mp 84–86 °C; R_f = 0.26 (silica gel, ethyl acetate/petroleum ether = 1:4); ¹H NMR (400 M, CDCl₃) δ 10.22 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 7.2 Hz, 1H), 7.40–7.46 (m, 2H), 4.22–4.38 (m, 4H), 3.03 (t, J = 6.4 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 1.28 (t, J = 7.2 Hz, 6H); ¹³C NMR (75 M, CDCl₃) δ 186.9, 167.9, 167.7, 140.1, 134.6, 126.7,

126.3, 125.8, 121.8, 119.6, 116.5, 63.5, 55.5, 30.9, 29.3, 13.8; HRMS (ESI) calcd for C₁₉H₁₉NO₆ (M + Na)⁺ 380.1105, found 380.1110; IR (KBr) ν 2992, 2862, 1751, 1735, 1664, 1551, 1455, 1387, 1311, 1239, 1220, 1187, 1141, 1075, 1015, 986, 947, 863, 831 cm⁻¹.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20572045) and the Ministry of Education of China (RFDF20070055022) for financial support.

Supporting Information Available: Detailed experimental procedure and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO900650H