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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

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Catalyzed by N-heterocyclic carbenes (NHCs), domino ringopening/redox amidation/cyclization reactions of the readily available formylcyclopropane 1,1-diesters with 2-chloro-1Hindole-3-carboaldehydes 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,³radical cyclizations,⁴nu-

⁽²⁾ Some selected examples include: (a) Li, G.; Huang, X.; Zhang, L. Angewa *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.





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

(5) Selected articles include: (a) Morales, C. L.; Pagenkopf, B. L. Org. Lett. 2008, 10, 157. (b) Tanino, H.; Fukuishi, 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) Bennasar, M.-L.; Zulaica, E.; Alonso, Y.; Vidal, B.; Vazquez, J. T.; Bosch, J. Tetrahedron: Asymmetry 2002. 13. 95.

⁽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.

⁽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) Khdour, 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.; Pairaudeau, 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) Tsotinis, 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.

^{(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.; Lamottke, K.; Vollhardt, K. P. C. Org. Lett. 2000, 2, 2479. (e) Beccalli, E. M.; Broggini, 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) Nicolaou, 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.

NHC-Catalyzed Ring-Opening Redox SCHEME 1. **Reactions of Activated FCPs**



carbenes (NHCs) have been efficiently applied as organocatalysts in a large number of umpolung chemical transformations.¹¹ Under catalysis of NHCs, activated formylcyclopropanes (FCPs) can undergo ring-opening-based redox esterification and amidation processes (Scheme 1).¹² Recently, we have reported a NHC-catalyzed domino reaction of 1,1-diactivated FCPs (with intermediate I as a formal 1,2-dipole) with salicylaldehyde, by which the coumarin skeleton can be directly constructed (Scheme 1).¹³ However, continuing effort to utilize intermediate II as a formal 1,4-dipole in organic syntheses follows our research interests. We envision that the reactions of intermediate II with 2-chloro-1H-indole-3-carboaldehyde would afford intermediate III, which would undergo subsequent intramolecular nucleophilic substitution to construct a 6-5-6 tricyclic pyrido[1,2-a]indole skeleton (Scheme 1). Herein we report this new type of domino ring-opening/redox amidation/cyclization reaction.

We initiated our investigations by examining the efficiency of various NHCs for the reaction of FCP 1,1-diester 2a with

TABLE 1. Optimization of the Reaction Conditions



^a Reaction conditions: 1.0 equiv of 1, 2.0 equiv of 2a, 40 mol % of the catalyst, and 2.0 equiv of the base, 60-70 °C, N₂ atmosphere. ^b Determined by recovered 1. ^c Isolated yields based on 1. ^d Anhydrous MgSO₄ was added as an additive. ^e 3.0 equiv of 2a was added.

2-chloro-1H-indole-3-carboaldehyde 1a in THF using DBU as a base. NHCs generated in situ from precursors A-D and F,G provided no desired product 3a with low conversion of 1a (Table 1, entry 1), while NHCs from precursor E, H, or I exhibited certain catalytic activity (Table 1, entry 2). Further screening of the reaction conditions suggested toluene, DBU (2.0 equiv), and catalyst H (40 mol %) as the optimal solvent, base, and catalyst, respectively (Table 1, entries 3-8). The addition of various nucleophilic co-catalysts commonly employed in acylation reactions, including HOBT, DMAP, ortho-nitrophenol, and imidazole,¹² failed to improve the reaction. However, slight improvement in the conversion of 1a and the yield was observed with prolonged reaction time and using anhydrous MgSO₄ as an additive (Table 1, entries 9 and 10). Increasing the amount of 2a to 3.0 equiv could also slightly improve the yield to 60% with 85% conversion of 1a, and this condition was selected as the optimal one (Table 1, entry 11). Notably, the leaving group X in 1 had no great impact on the reaction. Comparing to substrate 1a (X = Cl), a similar result was observed for 1b (X = Br) (Table 1, entry 12). It was surprising that no desired reactions happened for substrates 1c and 1d (Table 1, entry 13), indicating the significance of the formyl group. The structure of 3a was established by spectroscopic analysis and further confirmed by single-crystal X-ray analysis.¹⁴

With the optimal conditions in hand, we turned our attention to investigating the scope of substrates 1 and 2 (Table 2).

⁽¹⁰⁾ Some reviews include: (a) Danishefsky, S. Acc. Chem. Res. 1979, 12, 66. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C. Chem. Rev. 1989, 89, 165. (c) Reissig, H.-U.; Zimmer, R. Chem. Rev. 2003, 103, 1151. (d) Yu, M.; Pagenkopf, B. L. Tetrahedron 2005, 61, 321. (e) Wenkert, E. Acc. Chem. Res. 1980, 13, 27. A recent example includes: (f) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. Org. Lett. 2007, 9, 3331

⁽¹¹⁾ For reviews, please see: (a) Enders, D.; Balensiefer, T. Acc. Chem. Res. 2004, 37, 534. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. Angew. Chem., Int. Ed. 2007, 46, 2988. (c) Enders, D.; Niemeier, O.; Henseler, A. Chem. Rev. 2007. 107. 5606.

^{(12) (}a) Sohn, S. S.; Bode, J. W. Angew. Chem., Int. Ed. 2006, 45, 6021. (b) Bode, J. W.; Sohn, S. S. J. Am. Chem. Soc. 2007, 129, 13798. (c) Vora, H. U.; Rovis, T. J. Am. Chem. Soc. 2007, 129, 13796. (d) Ibrahem, I.; Zhao, G.-L.: Rios, R.; Vesely, J.; Sunden, H.; Dziedzic, P.; Cordova, A. Chem.-Eur. J. 2008 14, 7867. (e) Vesely, J.; Zhao, G.-L.; Bartoszewicz, A.; Cordova, A. Tetrahedron Lett. 2008, 49, 4209

TABLE 2. Investigation of the Reaction Scope⁴

$ \begin{array}{c} R^{1} 4 & 3 \\ 5 \\ 6 \\ 7 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 2 \\ 1 \\ 2 \\ 1 \\ 2 \\ 1 \\ 1$							
entry	1	\mathbb{R}^1	2	\mathbb{R}^2	\mathbb{R}^3	conv of $1 (\%)^b$	yield of $3 (\%)^c$
1	1a	Н	2a	Et	Н	85	3a , 60
2	1e	5-Cl	2a	Et	Η	75	3d , 41
3	1f	5-Br	2a	Et	Η	78	3e , 52
4	1g	5-I	2a	Et	Η	72	3f , 50
5	1h	6-C1	2a	Et	Η	53	3 g, 33
6	1i	5-Me	2a	Et	Η	>90	3h , 70
7	1j	5-Et	2a	Et	Η	88	3i , 76
8	1k	5- <i>i</i> -Pr	2a	Et	Η	81	3j , 72
9	1l	5-OMe	2a	Et	Η	>90	3k , 74
10	1m	7-Me	2a	Et	Η	56	NR
11	1n	$4,6-Me_2$	2a	Et	Η	59	31 , 37
12	1j	5-Et	2b	Me	Η	80	3m , 58
13	1a	Н	2b	Me	Η	68	3n , 50
14	1j	5-Et	2c	<i>i</i> -Pr	Η	59	30 , 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, N_2 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 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 ringopening/redox amidation/cyclization reaction between 2-chloro-1H-indole-3-carboaldehydes and the readily available FCP 1,1diesters. This methodology provides an efficient and direct access to a 6-5-6 tricyclic hydropyrido[1,2-*a*]indole 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.

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MgSO₄ and 56 mg (0.14 mmol) of catalyst **H**. 2-Chloro-1*H*-indole-3-carboaldehydes **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 $C_{19}H_{19}NO_6$ (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.

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

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