JOC*Note*

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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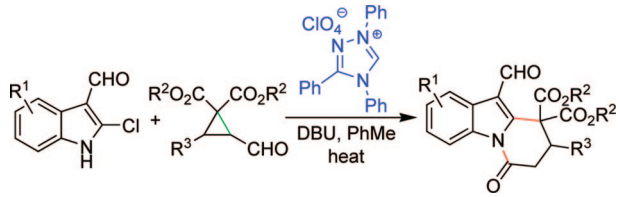

Catalyzed by N-heterocyclic carbenes (NHCs), domino ring-opening/redox amidation/cyclization reactions of the readily available formylcyclopropane 1,1-diesters with 2-chloro-1*H*-indole-3-carboaldehydes were reported. This methodology provides an efficient and direct construction of a 6−5−6 tricyclic 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,[3] radical cyclizations,[4] nucleophilic 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.

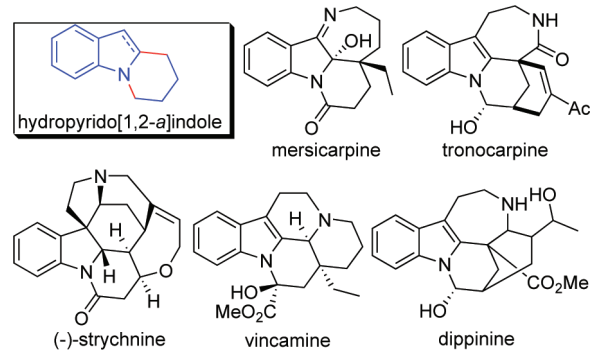

FIGURE 1. Selected typical alkaloids with a hydropyrido[1,2-*a*]indole skeleton.

Domino reactions[9] 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

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(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.

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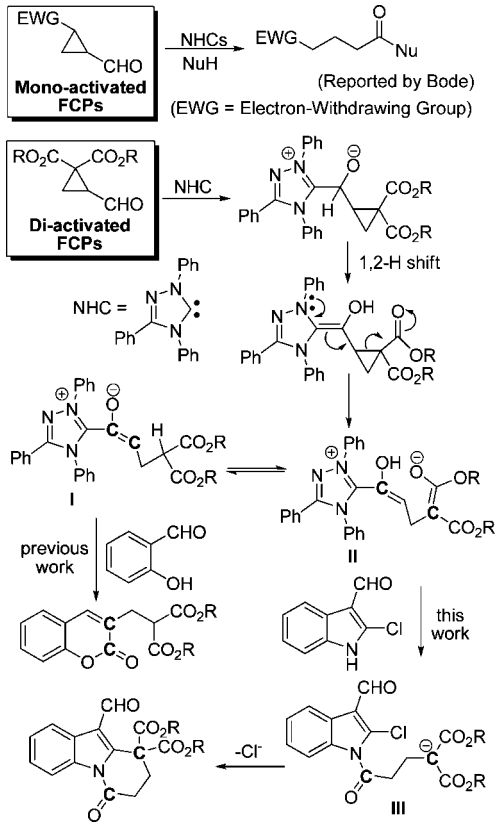
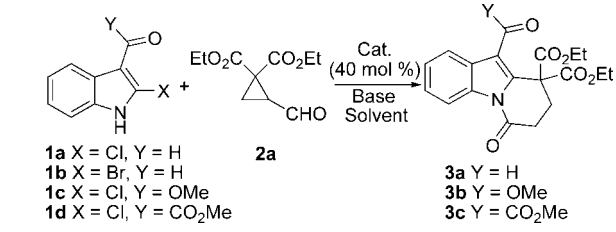
SCHEME 1. NHC-Catalyzed Ring-Opening Redox Reactions of Activated FCPs



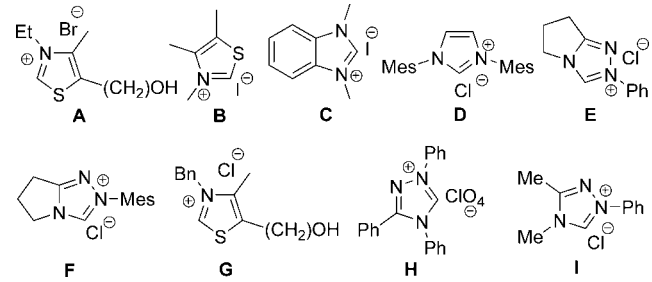
carbenes (NHCs) have been efficiently applied as organocatalysts in a large number of umpolung chemical transformations.[11] Under catalysis of NHCs, activated formylcyclopropanes (FCPs) can undergo ring-opening-based redox esterification and amidation processes (Scheme 1).[12] Recently, we have reported 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-1*H*-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]



entry	**1**	cat.	sol.	base	time (h)	conv of **1** (%)[b]	yield of **3a** (%)[c]
1	**1a**	**A**−**D**/**F**,**G**	THF	DBU	10	<10	0
2	**1a**	**E**/**H**/**I**	THF	DBU	16	<30	<20
3	**1a**	**H**	PhMe	DBU	18	65	44
4	**1a**	**H**	PhMe	Et_3N	16	<10	NR
5	**1a**	**H**	PhMe	K_2CO_3	18	70	39
6	**1a**	**H**	PhMe	Cs_2CO_3	24	68	40
7	**1a**	**H**	PhMe	NaH	20	<40	<20
8	**1a**	**H**	PhMe	*t*-BuOK	18	<40	<20
9[d]	**1a**	**H**	PhMe	DBU	20	62	48
10[d]	**1a**	**H**	PhMe	DBU	40	84	54
11[d,e]	**1a**	**H**	PhMe	DBU	40	85	60
12[d,e]	**1b**	**H**	PhMe	DBU	40	77	55
13[d,e]	**1c**/**1d**	**H**	PhMe	DBU	20	<20	NR



[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, N_2 atmosphere. [b] Determined by recovered **1**. [c] Isolated yields based on **1**. [d] Anhydrous $MgSO_4$ was added as an additive. [e] 3.0 equiv of **2a** was added.

2-chloro-1*H*-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 $MgSO_4$ 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).

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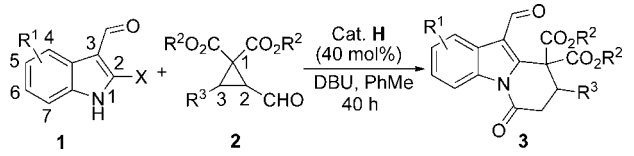
TABLE 2. Investigation of the Reaction Scope[a]



1 2 3

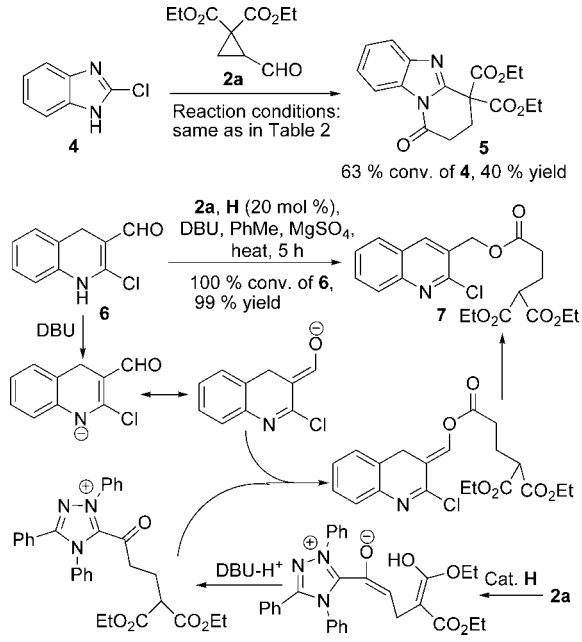
entry	1	R^1	2	R^2	R^3	conv of 1 (%)[b]	yield of 3 (%)[c]
1	**1a**	H	**2a**	Et	H	85	**3a**, 60
2	**1e**	5-Cl	**2a**	Et	H	75	**3d**, 41
3	**1f**	5-Br	**2a**	Et	H	78	**3e**, 52
4	**1g**	5-I	**2a**	Et	H	72	**3f**, 50
5	**1h**	6-Cl	**2a**	Et	H	53	**3g**, 33
6	**1i**	5-Me	**2a**	Et	H	>90	**3h**, 70
7	**1j**	5-Et	**2a**	Et	H	88	**3i**, 76
8	**1k**	5-*i*-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*-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 $MgSO_4$, PhMe, 60−70 °C, 40 h, N_2 atmosphere. [b] Determined by recovered **1**. [c] Isolated yields based on **1**.

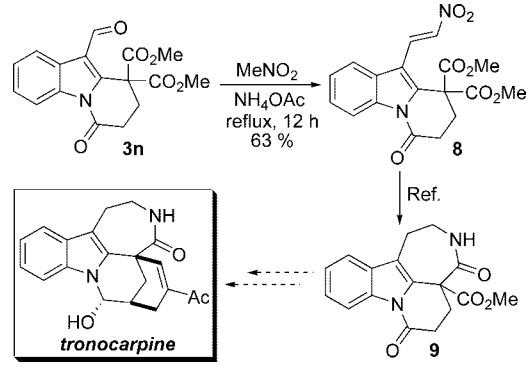
Substituents on the phenyl ring of substrate **1** significantly affected the yields as well as the conversions. Substrates **1** substituted with electron-withdrawing groups at the 5-position (Table 2, entries 2−4) reacted with **2a** in low to moderate yields and conversions, while substrates **1** 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 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 $MeNO_2$ 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-carboaldehydes and the readily available FCP 1,1-diesters. 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.

$MgSO_4$ 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 μL (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); ^{1}H NMR (400 M, $CDCl_3$) 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); ^{13}C NMR (75 M, $CDCl_3$) 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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