Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Zhongjiao Ren [a], Weiguo Cao [a b], Yeying Lu [a], Yun Wang [a] & Sihui Wang [a]

[a] Department of Chemistry, Shanghai University, Shanghai, China

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China

Version of record first published: 18 Aug 2008.

To cite this article: Zhongjiao Ren , Weiguo Cao , Yeying Lu , Yun Wang & Sihui Wang (2008): Ring-Expansion Reaction of Cyclopropane: A Novel Process for Synthesis of Bicyclic Dicarboximides from Cyclopropanedicarboximides and Carbon Nucleophile, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:13, 2215-2226

To link to this article: http://dx.doi.org/10.1080/00397910802031378

Synthetic Communications®, 38: 2215–2226, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802031378

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Ring-Expansion Reaction of Cyclopropane: A Novel Process for Synthesis of Bicyclic Dicarboximides from Cyclopropanedicarboximides and Carbon Nucleophile

Zhongjiao Ren,[1] Weiguo Cao,[1,2] Yeying Lu,[1] Yun Wang,[1] and Sihui Wang[1]

[1]Department of Chemistry, Shanghai University, Shanghai, China
[2]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China

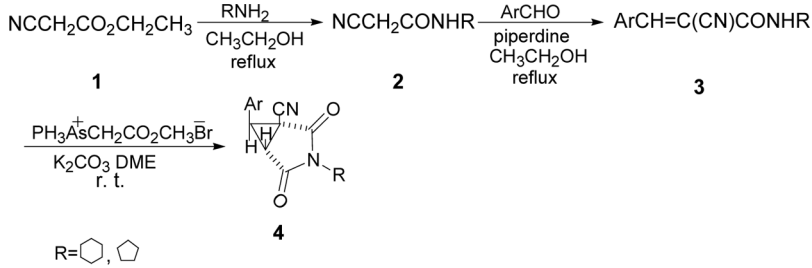
Abstract: The ring-expansion reaction of cyclopropane with carbon nucleophile was studied. The novel process for synthesis of bicyclic dicarboximides from cyclopropanedicarboximides with malononitrile or ethyl cyanoacetate was described.

Keywords: Bicyclic lactam; Cyclopropyl lactam; Malononitrile; Ring-expansion reaction

There has been increasing interest in cyclopropyl lactam, because it is an important structural unit in both natural and synthetic organic compounds.[1] However, up to now, less attention has been paid to the synthetic potential of the cyclopropyl lactam.

The ring-expansion reaction of cyclopropane bearing electron-withdrawing groups with nucleophiles is a methodology that has been widely applied in organic synthesis.[2] We have engaged in the ring-expansion reaction of cyclopropane with nitrogen nucleophile and reported the synthesis of 5-aryl-3-phenylpyrazole from cyclopropane with hydrazine,[3] lactam, and pyridone from cyclopropane with amine.[4] A survey of the

Received January 18, 2008
Address correspondence to Zhongjiao Ren, Department of Chemistry, Shanghai University, Shanghai 200444, China. E-mail: renrui198229@hotmail.com

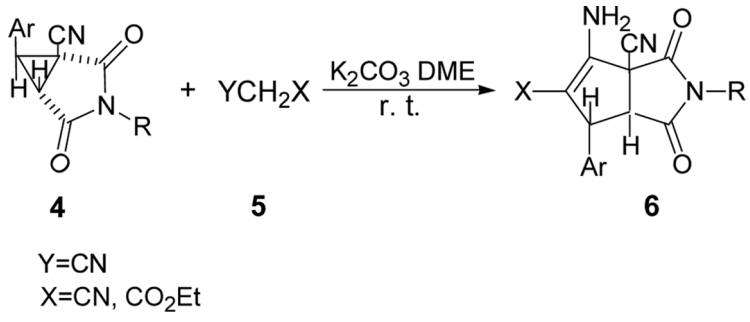


Scheme 1. Preparation of cyclopropanedicarboximindes 4.

literature revealed that ring-expansion reaction of cyclopropane with carbon nucleophile was rarely reported.

The formation of a carbon–carbon bond is the essence of organic chemistry. Therefore, we turned our attention to exploring the synthetic utility of the ring-expansion reaction of cyclopropyl lactam with the carbon nucleophile. Here we report a novel process for synthesis of bicyclic dicarboximides from cyclopropanedicarboximides with malononitrile or ethyl cyanoacetate in the presence of K_2CO_3 (Scheme 2).

We began by preparing cyclopropyl lactam. We have reported the approach for synthesis of cyclopropane derivatives with olefin and triphenylarsonium salt.[5] According to our reported approach, the synthesis of cyclopropyl lactam is outlined in Scheme 1. The ammonolysis of $NCCH_2CO_2CH_2CH_3$ **1** with primary aliphatic amine provided amide **2**, and subsequent Knoevenagel condensation of aldehyde with amide gave olefin **3**. The cyclopropanedicarboximides **4** were obtained via cyclopropanation reaction of olefins with triphenylarsonium salt. The results of preparing cyclopropanedicarboximides are shown in Table 1.



Scheme 2. Synthesis of bicyclic dicarboximides 6.

Table 1. Synthesis of cyclopropanedicarboximides from olefins and triphenylarsonium salt

Entry	Ar	R	Yield[a] (**4**) (%)
1	4-ClC_6H_4	cyclohexyl	**a** 68
2	4-BrC_6H_4	cyclohexyl	**b** 62
3	4-$CH_3OC_6H_4$	cyclohexyl	**c** 60
4	4-$CH_3C_6H_4$	cyclohexyl	**d** 50
5	C_6H_5	cyclohexyl	**e** 63
6	4-$CH_3OC_6H_4$	cyclopentyl	**f** 78
7	4-$CH_3C_6H_4$	cyclopentyl	**g** 75

[a]Isolated yield.
The results of Table 1 relate to Scheme 1.

It should be emphasized that the expected cyclopropanedicarboximide **4** was not obtained when the amines were n-propylamine, iso-propylamine, and n-butylamine.

The structures of compounds **4a–g** were confirmed by ^{1}H NMR, MS, IR, elemental analysis, and X-ray crystallographic analyses Fig. 1). The *trans* configurations of the compounds **4a–g** were also supported by comparison of the coupling constant of two protons situated at adjacent carbon atoms in the cyclopropane ring. It has been reported that the cyclopropyl protons with a *cis* relationship have larger coupling constants (~7–10Hz), whereas those with a *trans* relationship have smaller coupling constants (~ 3–7Hz).[6] The coupling constants of cyclopropanes **4a–g** were 4.2–4.7 Hz.

The most general means of generating carbon nucleophiles involve removal of a proton from an active methylene compound by a base. First, we tested some inorganic bases such as NaOH, K_2CO_3, and $NaHCO_3$. In

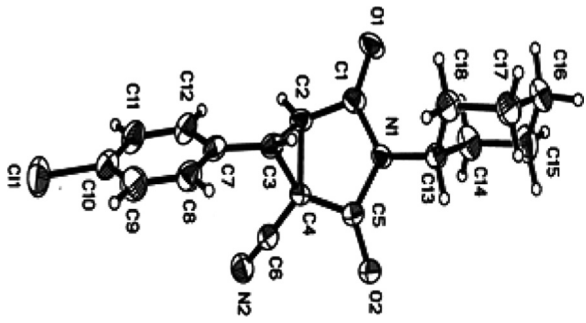


Figure 1. X-ray crystal structure of compound **4a**.

the model experiment, the mixture of cyclopropanedicarboximide **4a** (1 equiv), malononitrile **5** (1 equiv), and base (3 equiv) in dimethoxyethane (DME) was stirred at room temperature. The completion of the reaction was determined by thin-layer chromatography (TLC). When NaOH was employed as base, unidentified complex mixtures were obtained. No reaction occurred in the presence of $NaHCO_3$. The bicyclic dicarboximide **6a** was obtained in 70% yield when K_2CO_3 used a base. Then we examined the reaction temperature. When temperature raised, the reaction solution became a deep color and a complex mixture appeared. At 80°C, no desired compound **6a** was afforded (Table 2, entries 13). At 40°C, the compound **6a** was given in 56% yield (Table 2, entry 12). It is obvious that the high reaction temperatures do not favor reaction.

To investigate the scope of this reaction, a variety of cyclopropanedicarboximides and active methylene compounds were examined. The results are shown in Table 2. The reaction of cyclopropanedicarboximide **4** with malononitrile proceeded smoothly to give corresponding bicyclic dicarboximides (**6a–g**) in 60–82% yields under the optimized condition (Table 2, entries 1–7). The desired bicyclic lactams were afforded from cyclopropanedicarboximide **4** and ethyl cyanoacetate, but the their yields were lower (Table 2, entries 8, 9). No reaction was observed when the acetylacetone and ethyl acetoacetate were employed as carbon nucleophiles in the presence of K_2CO_3 (Table 2, entries 10, 11). These results suggested that no significant concentration of carbanion of ethyl cyanoacetate was produced, and the deprotonation of acetylacetone and ethyl acetoacetate was difficult in the presence of weakly basic K_2CO_3.

Table 2. Synthesis of bicyclic dicarboximides **6a–i**

Entry	Ar	R	Y	X	Temp.°C	Yield[a] of **6** (%)
1	4-ClC_6H_4	Cyclohexyl	CN	CN	rt	**6a** 70
2	4-BrC_6H_4	Cyclohexyl	CN	CN	rt	**6b** 60
3	4-$CH_3OC_6H_4$	Cyclohexyl	CN	CN	rt	**6c** 71
4	4-$CH_3C_6H_4$	Cyclohexyl	CN	CN	rt	**6d** 76
5	C_6H_5	Cyclohexyl	CN	CN	rt	**6e** 80
6	4-$CH_3OC_6H_4$	Cyclopentyl	CN	CN	rt	**6f** 82
7	4-$CH_3C_6H_4$	Cyclopentyl	CN	CN	rt	**6g** 80
8	4-ClC_6H_4	Cyclohexyl	CN	CO_2Et	rt	**6h** 50
9	4-$CH_3OC_6H_4$	Cyclohexyl	CN	CO_2Et	rt	**6i** 43
10	4-ClC_6H_4	Cyclohexyl	$COCH_3$	$COCH_3$	rt	0
11	4-ClC_6H_4	Cyclohexyl	$COCH_3$	CO_2Et	rt	0
12	4-ClC_6H_4	Cyclohexyl	CN	CN	40	**6a** 56
13	4-ClC_6H_4	Cyclohexyl	CN	CN	80	**6a** 0

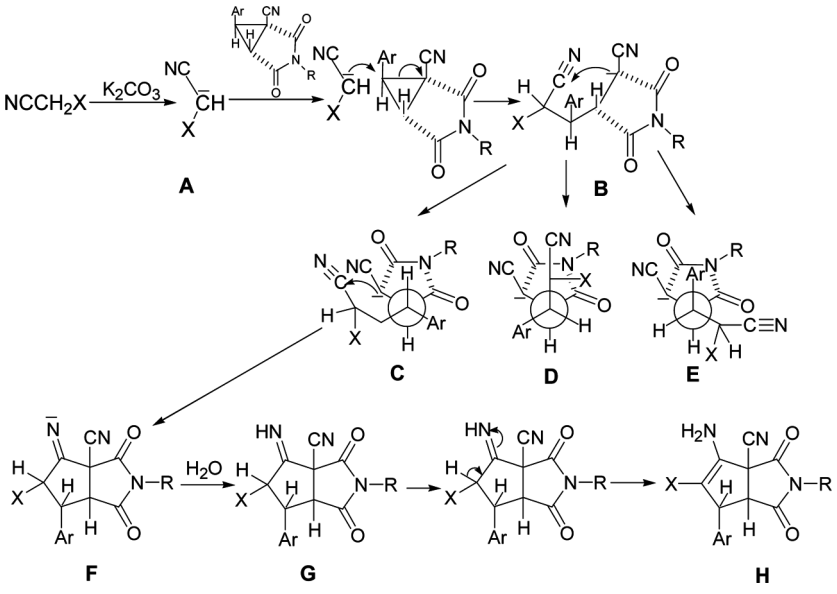
[a]Isolated yield.

The results of Table 2 relate to Scheme 2.

The structures of compounds **6a–i** were confirmed by ^{1}H NMR, MS, IR, and elemental analysis. The *trans* configuration of the compound **6** was assigned by nuclear overhauser effect (NOE) experiment. Interestingly, this ring-expansion reaction is highly stereoselective. In all cases, the *trans* configuration compound **6** is obtained as sole product, and no *cis* isomer is observed.

A plausible mechanism for the formation of product **6** is shown in Scheme 3. First, the carbanion **A** is generated by the deprotonation of active methylene compound with K_2CO_3 used a base and subsequent the ring-expansion reaction of cyclopropane with **A** occurs to give carbanion **B**, which is stabilized by cyano and amide groups. The three possible conformers (**C**, **D**, and **E**) may be given from **B**, which could lead to a *trans* or *cis* isomer. It is obvious that the ring-closure reaction could not take place through conformers **D** and **E**. So the conformation **C** controls reaction pathway to generate *trans* configuration product **6**. Next, the bicyclic intermediate **F** is formed via the nucleophilic attack of the carbanion **C** to cyano group followed by the protonation of the intermediate **F** to provide imine **G**. Then the product **H** is afforded through the rearrangement of the imine **G**.

In conclusion, the ring-expansion reaction of cyclopropane with carbon nucleophile was studied and the novel process for synthesis of bicyclic dicarboximides from cyclopropanedicarboximides with malononitrile or ethyl cyanoacetate was achieved.



Scheme 3. Proposed mechanism for the formation of 6.

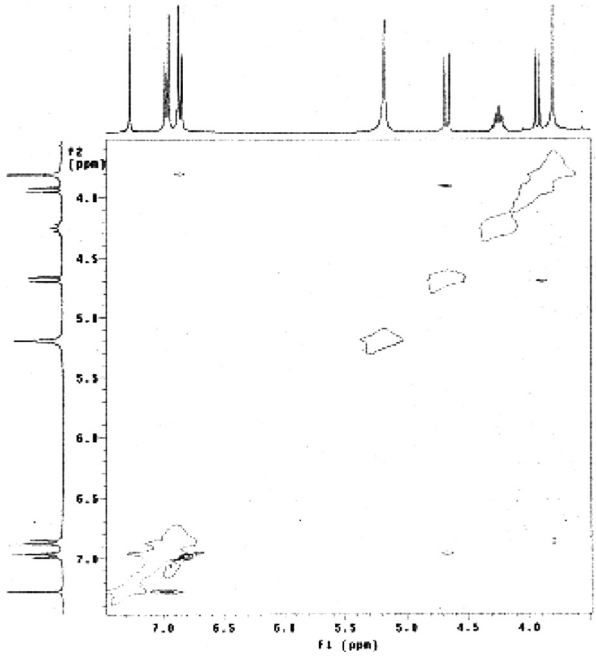


Figure 2. NOE spectrum of compound **6f**.

EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and used without purification. All melting points were uncorrected. Melting points were determined on WRS-1 digital melting-point apparatus made by Shanghai Physical Instrument Factory (SPOIF), China. IR spectra were measured in KBr on a PE-580B spectrometer. ^{1}H NMR spectra were recorded at a Bruker AM-300, using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were obtained on the Agilent 5973 N spectrometer. Elemental analyses were measured on the Elemental Vario EL III. X-ray crystal data sets were collected with a Bruker Smart Apex2 CCD.

General Procedure

Method A for Preparing 5,6-*trans*-dihydro-6-aryl-3-cyclics-2,4-dioxo-3aza-bicyclo[3,1,0]hexan-1-carbonitrile **4a–g**

A mixture of methoxycarbonylmethyltriphenylarsonium bromide (0.505 g, 1.1 mmol), arylidenecyanoactamides **3** (1 mmol), K_2CO_3 (0.165 g, 1.2 mmol), and a trace of water was stirred at room temperature in dimethoxyethane

(5 mL) for several hours. The completion of the reaction was determined by TLC. The solid suspended in DME was filtered off, and the solvent was removed off under reduced pressure at room temperature. The residue was purified by a silica-gel chromatographic column with petroleum ether–ethyl acetate (v:v 3:1) as eluant, and the crude product **4** was obtained. The crude product **4** was washed by a small amount of 95% ethanol and recrystallized by 95% ethanol.

Method B for Preparing 6,6a-*trans*-Dihydro-6-aryl-4-amino-2-cycloalkyl-1,3-dioxo-cyclopentene-4[c]pyrrole-3a,5-dicarbonitrile (6a-g) and 4,4a-*trans*-Dihydro-4-aryl-6-amino-6a-cyano-2-cyclohexyl-1,3-dioxo-cyclopentene-5[c]pyrrole-,5-dicarboxylic Acid Ethyl Ester **6h–i**

A mixture of 5,6-trans-dihydrogen-6-aryl-3-cyclics-2,4-dioxo-3aza-bicyclo[3,1,0]hexan-1-carbonitrile **4** (1 mmol), malononitrile or ethyl cyanoacetate (0.66 g or 0.113 g, 1 mmol), and K_2CO_3 (0.414 g, 3 mmol) was stirred at room temperature in 5 mL of DME for several hours. The completion of the reaction was determined by TLC. The solid suspended in DME was filtered off, and the solvent was removed off under reduced pressure at room temperature. The residue was purified by a silica-gel chromatographic column with petroleum ether–ethyl acetate (v:v 3:1) as eluant, and the crude product **6** was obtained. The crude product **6** was washed by a small amount of 95% ethanol and recrystallized by 95% ethanol.

Data

5,6-*trans*-Dihydro-3aza-3-cyclohexyl-2,4-dioxo-6-(4-chlorophenyl) bicyclo[3,1,0]hexan-1-carbonitrile **(4a)**

White solid, mp 191–192°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18–1.38 (m, 3H), 1.58–1.70 (m, 3H), 1.84–1.88 (m, 2H), 2.00–2.13 (m, 2H), 3.09 (d, $J = 4.4$ Hz, 1H), 3.43 (d, $J = 4.4$ Hz, 1H), 3.82–3.93 (m, 1H), 7.22 (d, $J = 8.5$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H); IR (KBr) 2249, 1710, 1599 cm^{-1}; MS (EI, 70 eV) m/z (%): 330 ($M^+ + 2$, 1), 329 ($M^+ + 1$, 2), 328 (M^+, 3), 301 (100), 219 (78), 207 (65), 203 (47), 190 (64), 140 (43) 55 (47), 41 (40). Anal. calcd. for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 65.92; H, 5.43; N, 8.30.

5,6-*trans*-Dihydro-3aza-3-cyclohexyl-2,4-dioxo-6-(4-bromophenyl) bicyclo[3,1,0]hexan-1-carbonitrile **(4b)**

White solid, mp 186–187°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19–1.38 (m, 3H), 1.56–1.70 (m, 3H), 1.84–1.88 (m, 2H), 2.00–2.13

(m, 2H), 3.07 (d, $J = 4.7$ Hz, 1H), 3.42 (d, $J = 4.7$ Hz, 1H), 3.73–3.92 (m, 1H), 7.16 (d, $J = 8.5$ Hz, 2H), 7.58 (d, $J = 8.5$ Hz, 2H); IR (KBr) 2248, 1710, 1594 cm^{-1}; MS (EI, 70 eV) m/z (%): 249 (55), 247 (58), 168 (100), 140 (83), 67 (30), 55 (77), 43 (38), 41 (72). Anal. calcd. for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.51. Found: C, 58.04; H, 4.60; N, 7.40.

5,6-trans-Dihydro-3aza-3-cyclohexyl-2,4-dioxo-6-(4-methoxyphenyl) bicyclo[3,1,0]hexan-1-carbonitrile **(4c)**

White solid, mp 174–175°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22–1.33 (m, 3H), 1.59–1.65 (m, 3H), 1.83–1.87 (m, 2H), 2.05–2.09 (m, 2H), 3.09 (d, $J = 4.2$ Hz, 1H), 3.42 (d, $J = 4.2$ Hz, 1H), 3.83 (s, 3H), 3.84–3.89 (m, 1H), 6.93 (d, $J = 8.4$ Hz, 2H), 7.18 (d, $J = 8.4$ Hz, 2H); IR (KBr) 2049, 1710, 1609 cm^{-1}; MS (EI, 70 eV) m/z (%): 324 (M^+, 6), 200 (15), 199 (100), 184 (6), 171 (8), 156 (17), 128 (14), 41 (6). Anal. calcd. for $C_{19}H_{20}N_2O_3$ C, 70.35; H, 6.21; N, 8.64. Found: C, 70.31; H, 6.28; N, 8.37.

5,6-*trans*-Dihydro-3aza-3-cyclohexyl-2,4-dioxo-6-(4-methylphenyl) bicyclo[3,1,0]hexan-1-carbonitrile **(4d)**

White solid, mp 161–162°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18–1.37 (m, 3H), 1.59–1.69 (m, 3H), 1.83–1.87 (m, 2H), 2.00–2.12 (m, 2H), 2.36 (s, 3H), 3.08 (d, $J = 4.4$ Hz, 1H), 3.43 (d, $J = 4.4$ Hz, 1H), 3.82–3.93 (m, 1H), 7.14 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 8.2$ Hz, 2H); IR (KBr) 2249, 1712, 1616 cm^{-1}; MS (EI, 70 eV) m/z (%): 308 (M^+, 1), 184 (15), 183 (100), 182 (7), 155 (6), 154 (9), 140 (14), 128 (4), 127 (5). Anal. calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.99; H, 6.69; N, 9.01.

5,6-*trans*-Dihydro-3aza-3-cyclohexyl-2,4-dioxo-6-phenyl-bicyclo[3,1,0]-hexan-1-carbonitrile **(4e)**

White solid, mp 197–198°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17–1.34 (m, 3H), 1.60–1.70 (m, 3H), 1.84–1.88 (m, 2H), 2.00–2.09 (m, 2H), 3.12 (d, $J = 4.2$ Hz, 1H), 3.47 (d, $J = 4.2$ Hz, 1H), 3.84–3.92 (m, 1H), 7.25–7.29 (m, 3H), 7.40–7.45 (m, 2H); IR (KBr) 2251, 1705, 1500 cm^{-1}; MS (EI, 70 eV) m/z (%): 170 (14), 169 (100), 141 (12), 140 (15), 115 (4), 114 (8), 55 (5), 41 (4). Anal. calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.66; H, 6.28; N, 9.28.

5,6-*trans*-Dihydro-3aza-3-cyclopentyl-2,4-dioxo-6-(4-methoxyphenyl) bicyclo[3,1,0]hexan -1-carbonitrile **(4f)**

White solid, mp 130–131°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.60 (m, 3H), 1.83–1.92 (m, 5H), 3.12 (d, $J = 4.7$ Hz, 1H), 3.42 (d, $J = 4.7$ Hz, 1H), 3.82 (s, 3H), 4.35–4.41 (m, 1H), 6.93 (d, $J = 8.6$ Hz, Hz, 2H), 7.19 (d, $J = 8.6$ Hz, 2H); IR (KBr) 2246, 1707, 1611 cm^{-1}; MS (EI, 70 eV) m/z (%): 310 (M^+, 5), 200 (15), 199 (100), 184 (9), 171 (2), 156 (30), 128 (25), 67 (9), 41 (16). Anal. calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.54; H, 5.88; N, 8.96.

5,6-*trans*-Dihydro-3aza-3-cyclopentyl-2,4-dioxo-6-(4-methylphenyl) bicyclo[3,1,0]hexan-1-carbonitrile **(4 g)**

White solid, mp 168–169°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53–1.61 (m, 3H), 1.83–1.92 (m, 5H), 2.37 (s, 3H), 3.12 (d, $J = 4.4$ Hz, 1H), 3.44 (d, $J = 4.4$ Hz, 1H), 4.36–4.41 (m, 1H), 7.14 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 8.2$ Hz, 2H); IR (KBr) 2244, 1707, 1518 cm^{-1}; MS (EI, 70 eV) m/z (%): 294 (M^+, 1), 184 (15), 183 (100), 155 (7), 154 (14), 140 (21), 128 (9), 127 (8), 41 (11). Anal. calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.52; H, 6.38; N, 9.40.

6,6a-*trans*-Dihydro-4-amino-6-(4-chloro-phenyl)-2-cyclohexyl-1,3-dioxo-cyclopentene-4[c]pyrrole-3a,5-dicarbonitrile **(6a)**

White solid, mp 296–297°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09–1.19 (m, 3H), 1.21–1.61 (m, 4H), 1.87–1.99 (m, 3H), 3.73–3.84 (m, 1H), 3.92 (d, $J = 10.4$ Hz, 1H), 4.69 (d, $J = 10.4$ Hz, 1H), 5.19 (br, s, 2H), 7.00 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.3$ Hz, 2H); IR (KBr) 3387, 3218, 2204, 1785, 1708, 1663 cm^{-1}; MS (EI, 70 eV) m/z (%): 396 ($M^+ + 2$, 9), 395 ($M^+ + 1$, 9), 394 (M^+, 26), 359 (17), 284 (19), 243 (35), 242 (27), 241 (100), 206 (47), 55 (19). Anal. calcd. for $C_{21}H_{19}ClN_4O_2$: C, 63.88; H, 4.85; N, 14.19. Found: C, 63.94; H, 4.71; N, 13.89.

6,6a-*trans*-Dihydro-4-amino-6-(4-bromo-phenyl)-2-cyclohexyl-1,3-dioxo-cyclopentene-4[c]pyrrole-3a,5-dicarbonitrile **(6b)**

White solid, mp 316–317°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10–1.22 (m 3H), 1.49–1.65 (m, 4H), 1.78–1.95 (m, 3H), 3.73–3.80 (m, 1H), 3.93 (d, $J = 10.4$ Hz, 1H), 4.60 (d, $J = 10.4$ Hz, 1H), 5.19 (br, s, 2H), 6.94 (d, $J = 8.2$ Hz, 2H), 7.48 (d, $J = 8.2$ Hz, 2H); IR (KBr) 3387,

3218, 2204, 1784, 1708, 1663 cm^{-1}; MS (EI, 70 eV) m/z (%): 440 ($M^+ + 2$, 7), 439 ($M^+ + 1$, 2), 438 (M^+, 7), 287 (66), 286 (26), 285 (65), 206 (68), 179 (27), 83 (52), 55 (100), 41 (60). Anal. calcd. for $C_{21}H_{19}BrIN_4O_2$: C, 57.41; H, 4.36; N, 12.75. Found: C, 57.38; H, 4.46; N, 12.35.

6,6a-*trans*-Dihydro-4-amino-2-cyclohexyl-6-(4-methoxy-phenyl)-1,3-dioxo-cyclopentene-4[c]pyrrole-3a,5-dicarbonitrile **(6c)**

White solid, mp 327–328°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13–1.25 (m, 3H), 1.47–1.63 (m, 4H), 1.76–1.91 (m, 3H), 3.73–3.84 (m, 4H), 3.90 (d, $J = 10.4$ Hz, 1H), 4.69 (d, $J = 10.4$ Hz, 1H), 5.15 (br, s, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.97 (d, $J = 8.6$ Hz, 2H); IR (KBr) 3394, 3218, 2208, 1782, 1707, 1665 cm^{-1}; MS (EI, 70 eV) m/z (%): 391 ($M^+ + 1$, 6), 390 (M^+, 25), 238 (21), 237 (100), 236 (24), 222 (20), 108 (16), 55 (47), 41 (31). Anal. calcd. for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.55; H, 5.44; N, 14.68.

6,6a-*trans*-Dihydro-4-amino-2-cyclohexyl-6-(4-methyl-phenyl)-1,3-dioxo-cyclopentene-4[c]pyrrole-3a,5-dicarbonitrile **(6d)**

White solid, mp 279–280°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09–1.24 (m, 3H), 1.47–1.63 (m, 4H), 1.80–1.96 (m, 3H), 2.33 (s, 3H), 3.73–3.81 (m, 1H), 3.91 (d, $J = 10.5$ Hz, 1H), 4.67 (d, $J = 10.5$ Hz, 1H), 5.15 (br, s, 2H), 6.93 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H); IR (KBr) 3391, 3219, 2204, 1785, 1708, 1663 cm^{-1}; MS (EI, 70 eV) m/z (%): 375 ($M^+ + 1$, 4), 374 (M^+, 17), 222 (21), 221 (100), 220 (19), 206 (21), 83 (9), 55 (28), 42 (18). Anal. calcd. for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.89; H, 5.92; N, 14.69.

6,6a-*trans*-Dihydro-4-amino-2-cyclohexyl-6-(phenyl)-1,3-dioxo-cyclopentene-4[c]pyrrole-3a, 5-dicarbonitrile **(6e)**

White solid, mp 252–253°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03–1.25 (m, 3H), 1.42–1.85 (m, 4H), 1.85–1.98 (m, 3H), 3.70–3.81 (m, 1H), 3.92 (d, $J = 10.5$ Hz, 1H), 4.70 (d, $J = 10.5$ Hz, 1H), 5.23 (br, s, 2H), 7.05–7.7 (m, 2H), 7.33–7.38 (m, 3H); IR (KBr) 3397, 3219, 2203, 1786, 1712, 1661 cm^{-1}; MS (EI, 70 eV) m/z (%): 361 ($M^+ + 1$, 3), 360 (M^+, 13), 250 (10), 208 (22), 207 (100), 206 (21), 83 (9), 55 (26), 41 (16). Anal. calcd. for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55. Found: C, 70.11; H, 5.48; N, 15.54.

6,6a-*trans*-Dihydro-4-amino-2-cyclopentyl-6-(4-methoxy-phenyl)-1,3-dioxo-cyclopentene-4[c]pyrrole-3a,5-dicarbonitrile **(6f)**

White solid, mp 235–236°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52–1.66 (m, 3H), 1.67–1.81 (m, 5H), 3.80 (s, 3H), 3.93 (d, $J = 10.4$ Hz, 1H), 4.24–4.27 (m, 1H), 4.67 (d, $J = 10.4$ Hz, 1H), 5.17 (br, s, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H); IR (KBr) 3388, 3219, 2208, 1783, 1709, 1665 cm^{-1}; MS (EI, 70 eV) m/z (%): 377 ($M^+ + 1$, 9), 376 (M^+, 33), 237 (95), 236 (28), 91 (30), 57 (25), 43 (37), 41 (54), 40 (100). Anal. calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.27; H, 5.45; N, 14.73.

6,6a-*trans*-Dihydro-4-amino-2-cyclohexyl-6-(4-methyl-phenyl)-1,3-dioxo-cyclopentene-4[c]pyrrole-3a,5-dicarbonitrile **(6g)**

White solid, mp 249–250°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50–1.65 (m, 3H), 1.67–1.84 (m, 5H), 2.33 (s, 3H), 3.93 (d, $J = 10.4$ Hz, 1H), 4.20–4.26 (m, 1H), 4.66 (d, $J = 10.4$ Hz, 1H), 5.20 (br, s, 2H), 6.92 (d, $J = 8.2$ Hz, 2H), 7.14 (d, $J = 8.2$ Hz, 2H); IR (KBr) 3390, 3218, 2208, 1786, 1712, 1664 cm^{-1}; MS (EI, 70 eV) m/z (%): 361 ($M^+ + 1$, 6), 360 (M^+, 24), 345 (12), 275 (15), 222 (19), 221 (100), 220 (19), 206 (22), 41 (20). Anal. calcd. for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55. Found: C, 69.90; H, 5.40; N, 15.74.

4,4a-*trans*-Dihydro-6-amino-4-(4-chloro-phenyl)-6a-cyano-2-cyclohexyl-1,3-dioxo-cyclopentene-5[c]pyrrole-,5-dicarboxylic acid ethyl ester **(6h)**

White solid, mp 193–194°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (tr, $J = 7.1$ Hz, 3H), 1.13–1.24 (m, 3H), 1.41–1.62 (m, 4H), 1.76–1.81 (m, 3H), 3.74–3.81 (m, 1H), 3.94 (d, $J = 10.7$ Hz, 1H), 4.00 (d, $J = 10.7$ Hz, 1H), 4.69 (q, $J = 7.1$ Hz, 2H), 6.10 (br, s, 2H), 7.22 (br, s, 4H); IR (KBr) 3472, 3319, 2248, 1786, 1709, 1676 cm^{-1}; MS (EI, 70 eV) m/z (%): 443 ($M^+ + 2$, 4), 442 ($M^+ + 1$, 3), 441 (M^+, 11), 290 (33), 288 (92), 217 (36), 216 (30), 215 (100), 55 (56), 41 (46). Anal. calcd. for $C_{23}H_{24}ClN_3O_4$: C, 62.51; H, 5.47; N, 9.51. Found: C, 62.56; H, 5.14; N, 9.30.

4,4a-*trans*-Dihydro-6-amino-6a-cyano-4-(4-methoxy-phenyl)-2-cyclohexyl-1,3-dioxo-cyclopentene-5[c]pyrrole-,5-dicarboxylic acid ethyl ester **(6i)**

White solid, mp 188–189°C (95% ethanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (tr, $J = 7.1$ Hz, 3H), 1.12–1.25 (m, 3H), 1.42–1.61 (m, 4H), 1.73–1.79

(m, 3H), 3.67–3.73 (m, 1H), 3.76 (s, 3H), 3.89 (d, $J = 10.7$ Hz, 1H), 3.96 (q,$J = 7.1$ Hz, 2H), 4.67 (d, $J = 10.7$ Hz, 1H), 6.08 (br, s, 2H), 6.08 (br, s, 4H); IR (KBr) 3446, 3335, 2254, 1785, 1709, 1676 cm^{-1}; MS (EI, 70 eV) m/z (%): 438 ($M^+ + 1$, 7), 437 (M^+, 23), 284 (54), 239 (41), 238 (41), 237 (32), 212 (25), 211 (100), 55 (57). Anal. calcd. for $C_{24}H_{27}N_3O_5$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.83; H, 5.85; N, 9.38.

ACKNOWLEDGMENT

Thanks are due to the National Natural Science Foundation of China and Natural Science Foundation of Shanghai for financial support (Nos. 20472047 and 04ZR 14060).

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