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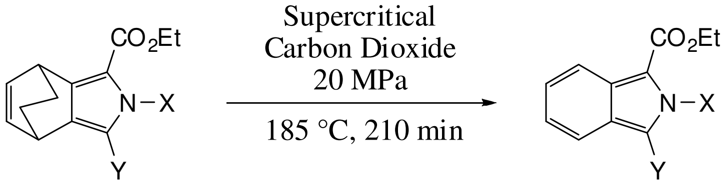

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Efficient synthesis of isoindoles using supercritical carbon dioxide

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ABSTRACT

Bicyclopyrroles were efficiently converted to the corresponding isoindoles by a retro Diels-Alder reaction in supercritical carbon dioxide. By adding ethylene gas as an oxygen scavenger, the isoindole yield was further improved.

Introduction

Isoindole has a simple skeleton in which benzene and pyrrole are fused and is a structural isomer of indole, which is found widely in nature. Isoindole derivatives and oligomers have been investigated as various functional materials. Isoindole derivatives are useful fluorescence labeling reagents[1] or antihypertensive agents.[2] For example, the oligomer benzopyrrolmethene has been used for red organic electroluminescence.[3] Tetrabenzoporphyrins have attracted attention as organic semi-conducting materials for field-effect transistors,[4] near-IR dyes,[5] solar cell materials,[6] and photosensitizers for photodynamic therapy.[7] Therefore, developing a method for synthesizing isoindoles is important (**Fig. 1**).

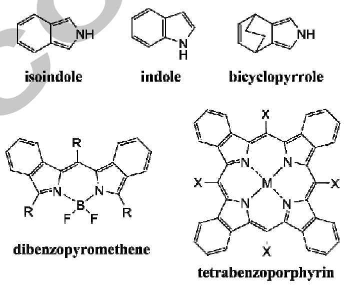

Figure 1. Isoindole and related compounds.

However, unsubstituted isoindole decomposes rapidly in air at room temperature because it has an exomethylene structure and readily reacts with oxygen in the air.[8] Therefore, introduction of substituents directly to isoindole is difficult and the synthesis of isoindole derivatives has been severely limited.[9] We focused on pyrrole fused with a bicyclo[2.2.2]octadiene skeleton (bicyclopyrrole: **1**). Bicyclopyrrole oligomers are converted quantitatively to the corresponding π-conjugated extended pyrrole oligomers by a retro Diels-Alder reaction. However, bicyclopyrrole derivatives are obtained very low yields (less than 15%) because the isoindole derivative quickly reacts with trace amounts of oxygen in high-boiling solvents.[10]

To eliminate the adverse effect of oxygen in the reaction system, we investigated using supercritical carbon dioxide. Supercritical carbon dioxide (T_c=304.2 K, P_c=7.4 MPa) is a special fluid that has both liquid and gas properties, and it is generated when the temperature and pressure of carbon dioxide are above its critical values.[11] Supercritical carbon dioxide can also dissolve organic compounds, making it useful as a reaction solvent in organic synthesis.[12] High-purity oxygen-free carbon dioxide is easy to obtain and has low toxicity. Therefore, we expected that isoindole derivatives could be synthesized efficiently by thermal decomposition of bicyclopyrrole in supercritical carbon dioxide.

Results and discussion

Bicyclopyrrole **1**, which was the starting material, was synthesized from *cis*-1, 2-dichloroethylene in five steps.[13] Bicyclopyrrole **1** was converted to α-bromobicyclopyrrole **2a** by reaction with *N*-bromosuccinimide. Bromobicyclopyrrole **2a** was also converted to α-phenylbicyclopyrrole **2b** by Suzuki coupling with phenylboronic acid. α-Bromobicyclopyrrole **2a** was reacted with copper cyanide to form α-cyanobicyclopyrrole **2c**. α-

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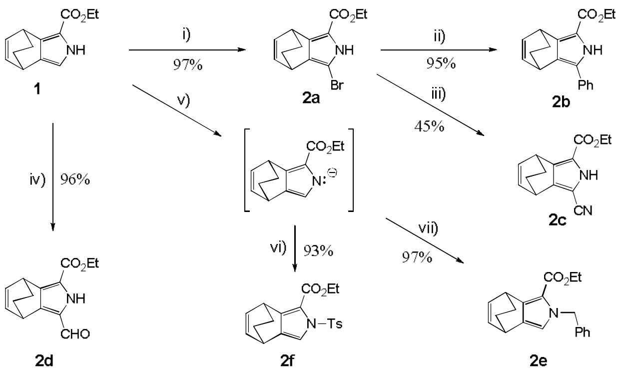
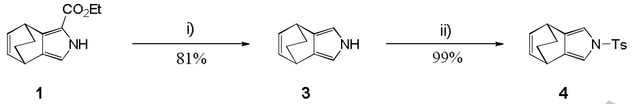
Formylbicyclopyrrole **2d** was synthesized from bicyclopyrrole **1** by a Vilsmeier formylation reaction. The ethyl ester group of bicyclopyrrole **1** was decarboxylated by heating in ethylene glycol in the presence of a strong base to obtain α-unsubstituted bicyclopyrrole **3**. The protons at the *N*-position of bicyclopyrroles **1** and **3** were removed with NaH, and the deprotonated bicyclopyrroles were treated with various halides to obtain the corresponding *N*-substituted bicyclopyrroles **2e**, **2f**, and **4** (**Schemes 1 and 2**).



Scheme 1. Reagents and Conditions: i) NBS, $CHCl_3$, reflux, 3 h; ii) $PhB(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, THF/H_2O (7:3), reflux, 24 h; iii) CuCN, DMF, reflux, 3 h; iv) $POCl_3$, DMF, rt, 3h; v) NaH, DMF, 0 °C, 30 min.; vi) TsCl, rt, 3 h; vii) $PhCH_2Br$, rt, 3 h.



Scheme 2. Reagents and Conditions: i) KOH, ethyleneglycol, 165 °C, 2 h; ii) NaH, DMF, 0 °C, 30 min., then TsCl, rt, 4 h.

The pyrolysis reaction of bicyclopyrroles **1** and **2a–e** in supercritical carbon dioxide was performed with the following reaction apparatus.[14] The experiments were conducted in a high-pressure reactor made from 316 stainless steel. The internal volume of the reactor was 50 cm^3. For the reaction, the bicyclopyrrole (50 mmol) and a magnetic stirrer were added to the reactor. The loaded reactor was placed in a gas chromatography oven (GC-7A, Shimadzu) and connected to the gas inlet line and gas outlet line (**Fig. 2**).

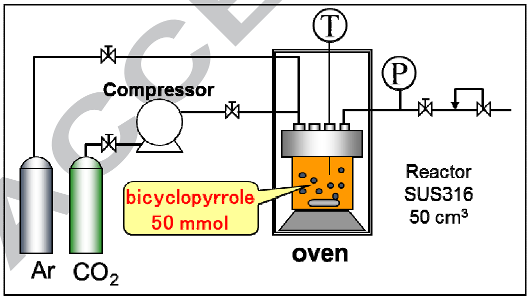
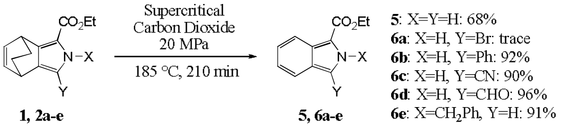


Figure 2. Schematic diagram of reactor.

The air in the reactor was gently purged with about 5 MPa of CO_2, and the pressure of the reactor was released to 0.1 MPa. After that, all valves connected to the reactor were closed. The heating was started from room temperature. When the temperature was raised to the reaction temperature, the valve connected to the compressor was opened and CO_2 was introduced to the reactor at the desired pressure, then the valve was closed again and then the magnetic stirrer was rotated. We defined that this time was the zero of reaction time. The pressure inside the reactor was almost constant. After the reaction time, the reactor was cooled and the CO_2 in the reactor was slowly released through the back pressure regulator. The products were purified by silica gel column chromatography and HPLC.

First, we examined the reaction conditions for bicyclopyrrole **1** in detail. The highest isolation yield of isoindole **5** (68% yield) was obtained when bicyclopyrrole **1** was heated in supercritical carbon dioxide at 185 °C for 210 min. When the decomposition reaction of bicyclopyrrole **1** was carried out at 220 ° C, the isolated yield of isoindole **5** was greatly decreased, and the reaction temperature was raised to 250 °C, black powder was obtained and isoindole **5** could not be isolated. However, an unexpected product, isoindole diester **9**, was isolated under all reaction conditions (yield of less than 1%). Next, bicyclopyrroles **2a–e** were also reacted under the same conditions (185 °C, 210 min). The isoindole yields varied greatly depending on the properties of the substituents. Bicyclopyrroles **2b–e** with an electron withdrawing group were converted to corresponding isoindole derivatives **6b–e** in high yields. In contrast, conversion of α-bromobicyclopyrroles **2a** and α-unsubstituted bicyclopyrrole **4** to isoindole were poorly controlled. In each of the reactions, α-bromoisoindole **6a** was obtained in extremely low yield, or a black powder that could not be assigned was obtained. Although the corresponding isoindoles were formed in the reaction system, decomposition occurred due to instability of the exomethylenic structure arising from the high electron density of the π-conjugated systems (**Scheme 3**, **Fig. 3**).



Scheme 3. Synthesis of isoindoles from bicyclopyrroles.

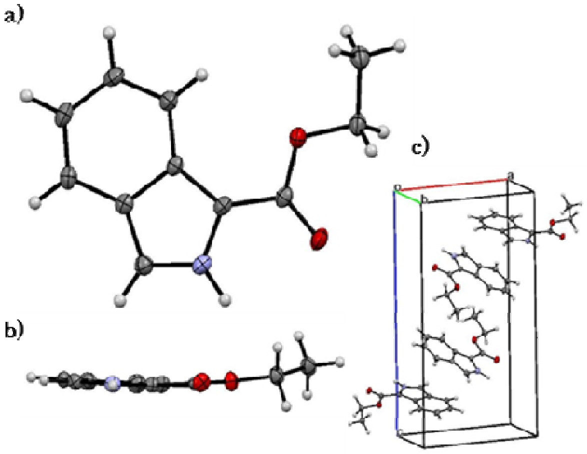
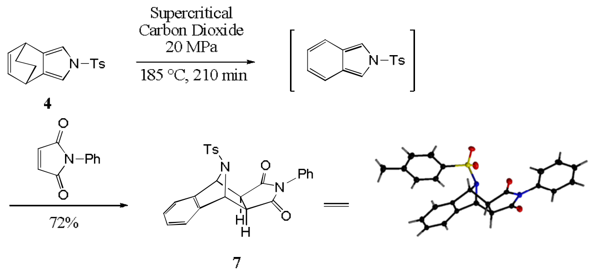


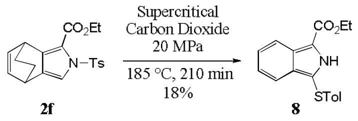
Figure 3. X-ray crystallographic analysis of isoindole **5**; a) front view, b) side view, c) crystal packing.

To confirm the formation of isoindole derivatives in the reaction system,[15] a retro Diels-Alder reaction of *N*-tosylated bicyclopyrrole **4** was performed by adding *N*-phenylmaleimide as a trapping agent for isoindole. As expected, Diels-Alder adduct **7** of *N*-tosylisoindole and *N*-phenylphthalimide was obtained in 72% yield and was found to be an *exo* Diels-Alder adduct by X-ray crystal structure analysis (**Scheme 4**).



Scheme 4. Synthesis of Diels-Alder Adduct of N-tosylisoindole and *N*-phenylmaleimide.

When *N*-tosylbicyclopyrrole **2f** was thermally decomposed in supercritical carbon dioxide, the expected isoindole was not obtained. Instead, only unexpected isoindole **8** was isolated and the structure of **8** was identified by X-ray crystal structure analysis. The sulfone of bicyclopyrrole **2f** was rearranged from the N-position to the α-position and reduced to a sulfide. The reaction mechanism is unknown (**Scheme 5**, **Fig. 4**).



Scheme 5. Formation of unexpected isoindole 8.

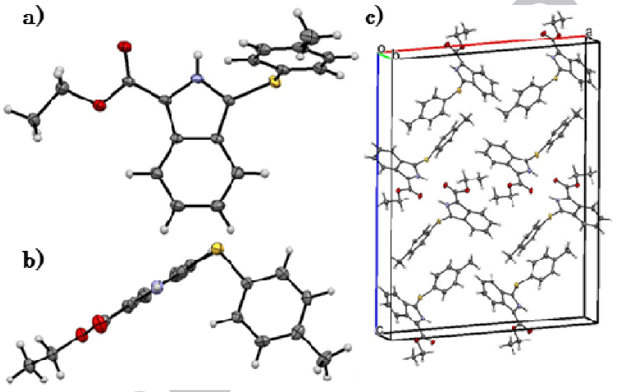
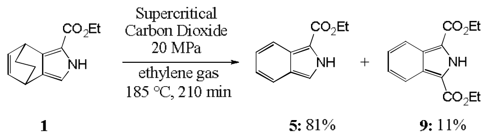


Figure 4. X-ray crystallographic analysis of isoindole **8**; a) front view, b) side view, c) crystal packing.

Even though the amount of oxygen in the reaction system was small, the yield of isoindole was very low. To remove residual oxygen, a small amount of ethylene gas was added as an oxygen scavenger and the thermal decomposition reaction of bicyclopyrrole **1** was carried out.[16] The ethylene gas prevented the decomposition of the product and the yield of isoindole **5** was greatly improved (81%). In addition, the yield of isoindole diester **9** also increased significantly (11%). We anticipate that added ethylene gas traps residual oxygen in the reaction system, but mechanism is unknown. We are conducting research to elucidate this reaction mechanism (**Scheme 6**, **Fig. 5**).



Scheme 6. Formation of isoindole diester **9**.

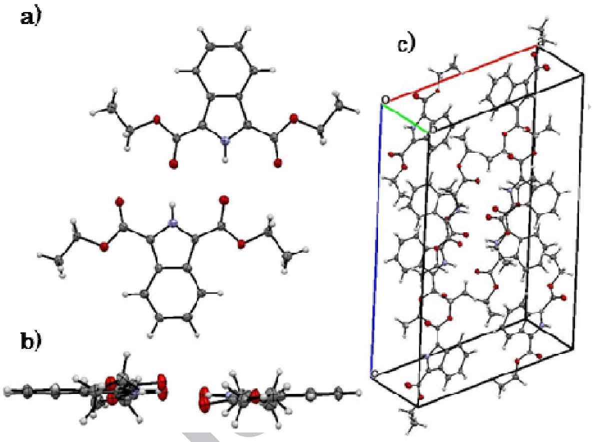


Figure 5. X-ray crystallographic analysis of isoindole diester **9**; a) front view, b) side view, c) crystal packing.

Conclusions

Bicyclopyrroles were transformed into isoindoles in good yield by a retro Diels-Alder reaction in supercritical carbon dioxide. Oxidative decomposition of the product was prevented by adding ethylene gas as an oxygen scavenger, greatly increasing the isolation yield of isoindoles. This synthesis method provides a new methodology for the synthesis of isoindole derivatives and contributes to the development of new functional organic materials with π-conjugated systems. We also demonstrated that supercritical carbon dioxide is useful as a reaction solvent for synthesizing sensitive organic compounds.

Acknowledgments

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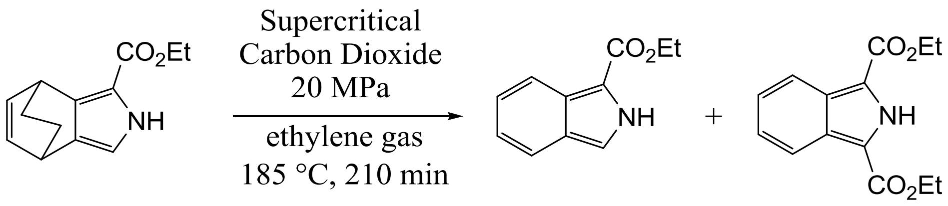
References and notes

1. Roth, M.; *Anal. Chem.*, **1971**, *43*, 880.
2. Press, J. B.; Wright Jr., W. B.; , Chan, P. S.; Marsico, J. W.; Haug, M. F.; Tauber, J.; Tomcufcik, A. S, *J. Med. Chem.*, **1986**, *29*, 816.
3. Wada, M.; Ito, S.; Uno, H.; Murashima, T.; Ono, N.; Urano, T.; Urano, Y.; *Tetrahedron Lett.*, **2001**, *42*, 6711; Urano, Y.; Ohno-Okumura, E.; Sakamoto, K.; Wada, M.; Ito, S.; Ono, N.; *Imag. Sci., J.*, **2001**, *48*, 147.
4. Aramaki, S.; Sakai, Y.; Ono, N. *Appl. Phys. Lett.* **2004**, *84*, 2085.
5. 5. Ito, S.; Murashima, T.; Uno, H.; Ono, N.; *Chem. Commun.*, **1998**, 1661; Ito, S.; Ochi, N.; Murashima, T.; Uno, H., Ono, N., *Heterocycles*, **2000**, *52*, 399.
6. Matsuo, Y.; Sato, Y.; Niinomi, T.; Soga, I.; Tanaka, H.; Nakamura, E. *J. Am. Chem. Soc.*, **2009**, *131*, 16048.
7. Hammerer, F.; Achelle, S.; Baldeck, P.; Philippe, M.; Fichou, M. P. J., *Phys. Chem.*, **2011**, *115*, 6503.
8. Bonnett, R.; Brown, R. F. C.; *Chem. Commun.*, **1972**, 393; Bornstein, J.; Remy, D. E.; Shields, J. E.; *Chem. Commun.*, **1972**,

1149; Priestley, G. M.; Warrener, R. N., *Tetrahedron Lett.*, **1972**, *42*, 4295.

9. Theilacker, W.; Bluhm, H. J.; Heitmann, W.; Kalenda, H.; Meyer, H. J.; *Ann. Chem.*, **1964**, *96*, 673; Emmett, J. C.; Veber, D. F.; Lwowski, W.; *Chem. Commun.*, **1965**, 272; Emmett, J. C.; Lwowski, W.; *Tetrahedron*, **1966**, *22*, 1011; Fryer, R. I.; Earley, J. V.; Sternbach, L. H.; *J. Am. Chem. Soc.*, **1966**, *88*, 3173; Ahmed, I.; Cheeseman, G. W. H.; Jaques, B.; Wallace, R. G., *Tetrahedron*, **1977**, *33*, 2255; Murashima. T, Tamai. R, Nishi. K, Nomura. K, Fujita. K, Uno. H, Ono. N, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 995; Ohmura, T.; Kijima, A.; Suginome, M., *Org. Lett.,* **2011,** *13*, 1238; Chrostowska, A.; Mazière, A.; Dargelos, A.; Graciaa, A.; Darrigan, C.; Weber, L.; Halama, J., *Eur. J. Inorg. Chem.,* **2013**, 5672; Green, A. P.; Turner, N. J.; O Reilly, E., *Angew. Chem. Int. Ed.* **2014**, *53*, 10714.
10. Uno, H.; Ito, S.; Wada, M.; Watanabe, H.; Nagai, M.; Hayashi, A.; Murashima, T.; Ono, N., *J. Chem. Soc., Perkin Trans. 1*, **2000**, 4347-4355.
11. Charles, A. E., *Nature*, **1996**, *383*, 313.
12. Brennecke, J. F.; Chateauneuf, J. E., *Chem. Rev.*, **1999**, *99*, 433; Licence, P.; Ke, J.; Sokolova, M.; Ross, S. K.; Poliakoff, M., *Green Chem.* **2003**, *5*, 99.
13. Ito, S.; Murashima, T.; Ono, N., *J. Chem. Soc., Perkin Trans. 1*, **1997**, 3161; Okujima, T.; Hashimoto, Y.; Jin, G.; Yamada, H.; Uno, H.; Ono, N., *Tetrahedron*, **2008**, *64*, 2405.
14. Sato, T.; Ito, S.; Yajima, Y.; Itoh, N., *J. Supercritical Fluids*, **2009**, *51*, 217.
15. Solé, D.; Serrano, O., *Org. Biomol. Chem.*, **2009**, *7*, 3382.
16. In the case of the experiment with ethylene, 0.1 MPa of ethylene gas was introduced to the reactor through the other introduction port before the introduction of CO_2.
17. Selected experimental data for bicyclopyrrole **2a**; Colorless crystal: m.p. = 145-148 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 9.00 (brs, 1H), 6.51-6.45 (m, 2H), 4.36-4.31 (m, 1H, q, 2H, *J* = 7.1 Hz), 3.80 (m, 1H), 1.59-1.43 (m, 4H), 1.39-1.36 (t, 3H, *J* = 7.05 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ = 161.1, 137.7, 135.7, 135.1, 130.7, 115.2, 95.8, 60.3, 34.0, 32.6, 26.4, 26.1, 14.5; Anal. calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73. Found: C, 52.57; H, 4.75; N, 4.71. For **2b**; Colorless crystal, m.p. = 147-150 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (brs, 1H), 7.51 (d, 2H), 7.42 (d, 2H), 7.28 (t, 1H), 6.54 (d, 2H), 4.41 (s, 1H), 4.33 (q, 2H, *J* = 7.1 Hz), 4.20 (s, 1H), 1.62-1.53 (m, 4H), 1.39 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.9, 138.2, 136.1, 135.5, 132.2, 129.1, 128.9, 127.4, 126.3, 114.0, 60.1, 33.9, 33.5, 26.9, 26.4, 14.7; MS (FAB+) m/z 294 [M$^+$+1]; Anal. calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.69; H, 6.56; N, 4.69. For **2c**; Colorless crystal, m.p. = 127-129 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.94 (brs, 1H), 6.51-6.46 (m, 2H), 4.44-4.37 (q, 2H, *J* = 7.1 Hz), 4.37 (s, 1H), 4.08 (s, 1H), 1.61-1.59 (d, 2H), 1.47-1.45 (d, 2H), 1.44-1.41 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.1, 141.1, 136.0, 135.6, 134.9, 118.2, 113.1, 96.3, 61.5, 33.7, 33.1, 26.3, 26.0, 14.5; MS (FAB+) m/z 243 [M$^+$+1]; Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.26; H, 5.71; N, 11.47. For **2d**; Colorless crystal, m.p. = 113-115 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 9.10 (s, 1H), 6.57-6.49 (m, 2H), 4.42 (s, 1H), 4.39-4.34 (q, 2H, *J* = 7.1 Hz), 4.28 (s, 1H), 1.67-1.60 (d, 2H), 1.51-1.49 (d, 2H), 1.41-1.49 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ178.6, 161.1, 141.1, 136.9, 136.0, 134.7, 125.2, 119.4, 61.1, 33.4, 32.7, 26.5, 26.1, 14.5; MS (FAB+) m/z 246 [M$^+$+1]; Anal. calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.66; H, 6.09; N, 5.72. For **2e**; Colorless crystal, m.p. = 78-82 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23-8.21 (m, 2H), 7.31 (m, 2H), 7.26-7.22 (m, 2H), 7.20-7.18 (m, 1H), 7.00-6.97 (m, 2H), 6.59 (s, 2H), 4.43-4.39 (q, 4H, *J* = 7.1 Hz), 1.44-1.41 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.2, 138.2, 128.4, 127.9, 126.9, 126.0, 125.5, 121.7, 118.3, 60.8, 50.6, 14.3; MS (ESI-TOF) m/z 352 [M+H]$^+$; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{22}NO_4$ [M+H]$^+$: 352.1543. Found: 352.1542. For **2f**; Colorless crystal, m.p. = 127-129 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84 (m, 2H), 7.29-7.27 (m,1H), 7.28 (m, 2H), 6.48-6.45 (m, 1H), 6.42-6.39 (m, 1H), 4.25 (m, 1H), 4.24-4.19 (m, 2H), 3.83 (m, 1H), 2.40 (s, 3H), 1.57-1.47 (m, 4H), 1.30-1.28 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.6, 144.2, 143.9, 136.9, 134.5, 131.1, 129.3, 127.8, 118.3, 116.4, 60.4, 33.9, 26.4, 25.5, 21.7, 14.3; MS (ESI-TOF) m/z 372 [M+H]$^+$; Anal. calcd for $C_{21}H_{20}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.46; H, 5.68; N, 3.82. For **4**; Colorless crystal, m.p. = 146-148 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, 2H), 7.23 (d, 2H), 6.75 (s, 2H), 6.38-6.35 (m, 2H), 3.71 (m, 2H), 2.36 (s, 3H), 1.52-1.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.3, 136.7, 136.3, 135.1, 134.6, 129.8, 129.3, 127.5, 126.4, 110.6, 108.1, 33.2, 32.7, 27.6, 26.6, 21.6; MS (ESI-TOF) m/z 300 [M+H]$^+$; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{18}NO_2S$ [M+H]$^+$: 300.1053. Found: 300.0867.
18. Selected experimental data for isoindole **5**; Colorless crystal, m.p. = 132-136 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.5 (brs, 1H), 8.09-8.07 (m, 1H), 7.68 (m, 1H), 7.49 (d, 1H, *J* = 3.0 Hz), 7.29-7.26 (m, 1H), 7.12-7.09 (m, 1H), 4.50-4.45 (t, 2H, *J* = 7.1 Hz), 1.49-1.46 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.2, 126.9, 125.8, 125.5, 122.2, 121.1, 120.6, 116.0, 111.6, 60.3, 14.7; MS (ESI-TOF) m/z 190 [M+H]$^+$; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{12}NO_2$ [M+H]$^+$: 190.0863. Found: 190.0845. For **6b**; Colorless crystal, m.p. = 138-139 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.82 (brs, 1H), 8.12 (d, 1H), 7.95 (d, 1H), 7.78 (d, 1H), 7.54 (t, 1H), 7.09 (t, 1H), 7.41 (t, 1H), 7.33 (t, 1H), 7.18 (t, 1H), 4.41 (q, 2H, *J* = 7.1 Hz), 1.44 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 131.6, 129.4, 128.1, 128.0, 127.4, 126.0, 125.9, 123.4, 123.1, 123.0, 121.1, 121.0, 60.5, 14.84; MS (ESI-TOF) m/z 266 [M+H]$^+$; Anal. calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.75; H, 5.50; N, 5.18. For **6c**; Colorless crystal , m.p. = 193-194 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.03 (brs, 1H), 8.17-8.13 (m, 1H), 7.80-7.77 (m, 1H), 7.40-7.35 (m, 2H), 4.56-4.52 (q, 2H, *J* = 7.1 Hz), 1.52-1.49 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.6, 131.1, 126.6, 126.1, 125.7, 121.7, 119.2, 117.2, 113.2, 97.0, 62.3, 14.6; MS (EI) m/z 214 [M+]; Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.06; H, 4.53; N, 13.01. For **6d**; Colorless crystal, m.p. = 163-165 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.29 (brs, 1H), 10.14 (s, 1H), 8.19-8.18 (d, 1H), 8.08-8.07 (d, 1H), 7.44-7.36 (m, 2H), 4.54-4.49 (q, 2H, *J* = 7.1 Hz), 1.50-1.47 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.1, 161.6, 129.9, 127.7, 127.6, 126.9, 124.8, 122.5, 119.7, 119.2, 62.2, 15.0; MS (ESI-TOF) m/z 218 [M+H]$^+$; Anal. calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.07; H, 5.07; N, 6.04. For **6e**; Colorless oil, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14-8.11 (m, 1H), 7.60-7.58 (m, 1H), 7.40 (s, 1H), 7.31-7.23 (m, 4H), 7.15-7.13 (m, 2H), 7.10-7.07 (m, 1H), 5.91 (s,2H), 4.40-4.36 (q, 2H, *J* = 7.0 Hz), 1.44-1.41 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.1, 138.6, 137.7, 129.1, 128.7, 128.1, 128.0, 127.9, 127.5, 125.7, 122.5, 121.6, 120.6, 60.1, 54.1, 14.9; MS (ESI-TOF) m/z 280 [M+H]$^+$; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{18}NO_2$ [M+H]$^+$: 280.1332. Found: 280.1146. For Diels-Alder adduct **7**; Colorless crystal, m.p. >250 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50-7.47 (m, 2H), 7.45-7.42 (m, 2H), 7.40-7.38 (m,2H), 7.23-7.21 (m, 2H), 7.14-7.14 (m, 2H), 7.05-7.04 (m, 2H), 7.05-7.04 (m, 2H), 7.00-6.99 (m, 2H), 5.48 (s, 2H), 3.05 (s, 2H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 143.7, 141.9, 135.0, 131.6, 129.3, 129.33, 129.29, 129.1, 127.8, 127.7, 126.4, 121.1, 66.3, 49.5, 21.5; MS (EI) m/z 444 [M+]; Anal. calcd for $C_{25}H_{20}N_2O_4S$: C, 67.55; H, 4.54; N, 6.30. Found: C, 67.34; H, 4.35; N, 6.32. For **8**; Colorless crystal, mp 149-151 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.33 (brs, 1H), 8.10-8.09 (d, 1H), 7.74-7.72 (m, 1H), 7.32-7.30 (m, 1H), 7.20-7.16 (m, 1H), 7.01 (s, 4H), 4.47-4.43 (q, 2H, *J* = 7.1 Hz), 2.26 (s, 3H), 1.47-1.44 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.6, 132.5, 130.1, 129.6, 128.0, 125.9, 123.6, 121.1, 120.2, 114.2, 60.6, 20.9, 14.6; MS (EI) m/z 311 [M+]; Anal. calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.33; H, 5.39; N, 4.52. For **9**; Gray crystal, m.p. = 118-120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.91 (brs, 1H), 8.15-8.12 (m, 2H), 7.33-7.30 (m, 2H), 4.51-4.46 (q, 4H, *J* = 7.1 Hz), 1.49-1.46 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 127.0, 125.7, 121.3, 115.9, 61.1, 14.5; MS (ESI-TOF) m/z 262 [M+H]$^+$; Anal. calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.60; H, 5.86; N, 5.30.
19. All measurements were made on a Bruker SMART-APEX II CCD plate detector with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of −173 °C and processed using the APEX II programs from Bruker.
20. Shelx-2013: Program for the refinement of crystal structures from diffraction data, University of Göttingen, Göttingen, Germany; "Crystal structure refinement with SHELXL". M. G. Sheldrick, *Acta Cryst.,* **2015**, *C71*, 3–15, DOI: org/10.1107/S2053229614024218.
21. CCDC 1526462 (**2a**), CCDC 1526461 (**2f**), CCDC 1526460 (**4**), CCDC 1526456 (**5**), CCDC 1526455 (**7**), CCDC 1526454 (**8**), and CCDC 1526453 (**9**) contain the 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.



1 **5:** 81% **9:** 11%

Scheme 6. Formation of isoindole diester **9**.

Highlights

Bicyclopyrroles were efficiently converted to the corresponding isoindoles by a retro Diels-Alder reaction in supercritical carbon dioxide.

By adding ethylene gas as an oxygen scavenger, the isoindole yield was further improved.

This synthesis method provides a new methodology for the synthesis of isoindole derivatives.