

INTRAMOLECULAR DIELS-ALDER REACTION OF 3-(1H-INDOL-3-YL)-2-
PROPENOATES: SYNTHESIS OF FUSED INDOLE COMPOUNDS

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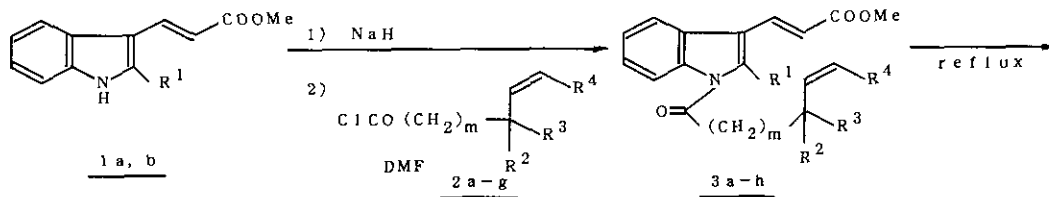
Abstract - Intramolecular Diels-Alder reaction of 3-(1H-indol-3-yl)-2-propenoates having the olefinic substituents at the 1-position of the indole ring gave stereoselectively fused indole compounds.

There have been many reports about the intermolecular Diels-Alder reaction of 3-vinylindoles.^{1,2} Recently, U. Pindur reviewed the intermolecular Diels-Alder reaction of 1- or 2-vinylindoles.³ However, very little is known about the intramolecular Diels-Alder reaction of 3-(1H-indol-3-yl)-2-propenoates.⁴ There are many naturally occurring fused indole compounds such as vinca alkaloids. Here, we report on the facile stereoselective synthesis of fused indole compounds using intramolecular Diels-Alder reaction of (*E*)- and (*Z*)-3-(1H-indol-3-yl)-2-propenoates (**3a-h** and **9a-c**) having olefinic substituents at the 1-position of the indole ring.

The (*E*)-propenoates **3a-h** were prepared by acylation of methyl (*E*)-3-(1H-indol-3-yl)-2-propenoates (**1a,b**) with compounds (**2a-g**).

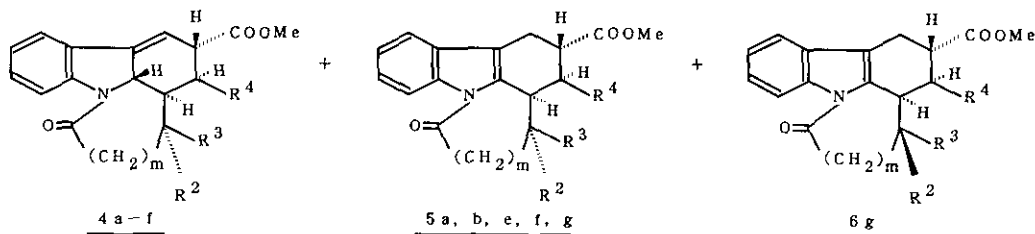
Intramolecular Diels-Alder reaction of **3a-h** was carried out under reflux in the appropriate solvent to indolines (**4a-f,7,8**) and indoles (**5a,b,e-g,6g**) shown in Scheme 1. The ratio of products depended on the reaction temperature, the number of *m*, R³ and R⁴. The results are shown in Table 1.

Reaction of **3a** under reflux in mesitylene afforded only the **4a** in 77.6% yield (Run 1). On the other hand reflux of **3a** in *o*-dichlorobenzene gave predominantly indole **5a** (Run 2). Because the indole type product **5a** is thermodynamically more stable than the indoline type product **4a**, the reaction in *o*-dichlorobenzene which has a higher boiling point than mesitylene seems to give **5a** predominantly.



a: R¹=H
b: R¹=Me

	R ¹	R ²	R ³	R ⁴	m		R ¹	R ²	R ³	R ⁴	m
a:	H	H	H	H	1	e:	H	H	-(CH ₂) ₃ -	-	1
b:	H	H	-(CH ₂) ₂ -	-	1	f:	H	Et	-(CH ₂) ₃ -	-	1
c:	H	Et	-(CH ₂) ₂ -	-	1	g:	H	H	-(CH ₂) ₄ -	-	1
d:	H	H	-(CH ₂) ₂ -	-	2	h:	Me	H	-(CH ₂) ₂ -	-	1



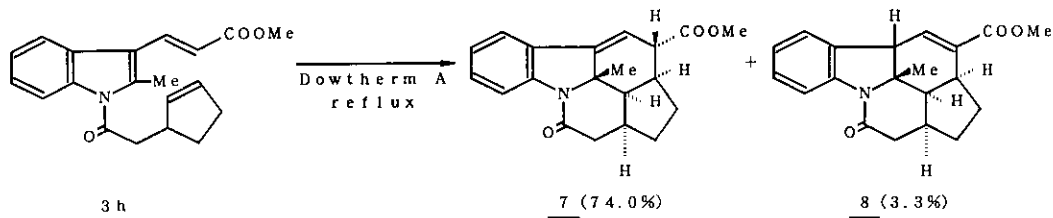
	R ²	R ³	R ⁴	m
a:	H	H	H	1
b:	H	-(CH ₂) ₂ -	-	1
c:	Et	-(CH ₂) ₂ -	-	1
d:	H	-(CH ₂) ₂ -	-	2
e:	H	-(CH ₂) ₃ -	-	1
f:	Et	-(CH ₂) ₃ -	-	1

	R ²	R ³	R ⁴	m
a:	H	H	H	1
b:	H	-(CH ₂) ₂ -	-	1
e:	H	-(CH ₂) ₃ -	-	1
f:	Et	-(CH ₂) ₃ -	-	1
g:	H	-(CH ₂) ₄ -	-	1

	R ²	R ³	R ⁴	m
g:	H	-(CH ₂) ₄ -	-	1

Scheme 1.

Diels-Alder reaction of **3b,c,d,f** under reflux in mesitylene gave only **4b,c,d,f** respectively (Runs 3, 4, 5, 7). However, **3e** afforded a mixture of **4e** and **5e** in 62.5 and 11.5 % yields, respectively (Run 6). On the other hand, cyclization of **3g** afforded **5g** and its epimer **6g** in 21.7 and 58.3% yields, respectively (Run 8). Cyclization of **3h** gave **7** and double bond migrated product **8** under reflux in Dowtherm A in 74.0 and 3.3 % yields, respectively, but the reaction did not proceed under reflux in mesitylene.

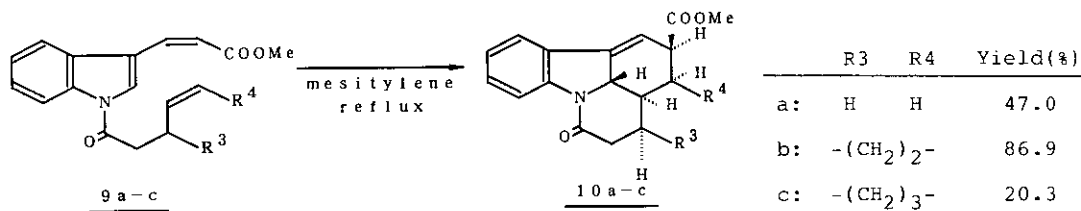


Scheme 2.

Table 1. Results of Intramolecular Diels-Alder Reaction

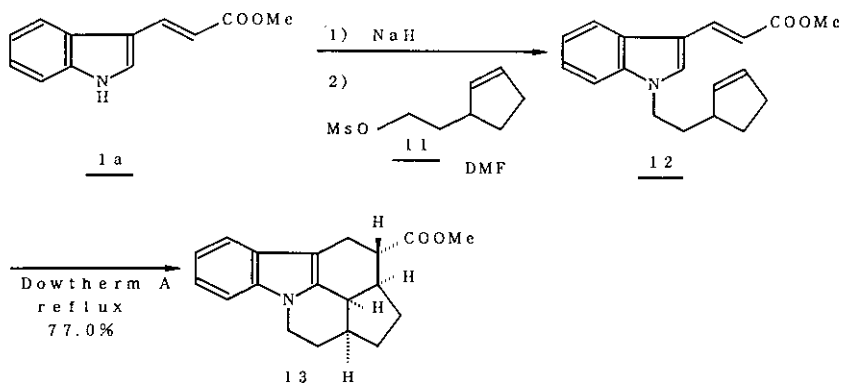
Run	Starting Compd	reaction					Yield(%)			
		R ²	R ³	R ⁴	m	solvent	time(hr.)	4	5	6
1	3a	H	H	H	1	mesitylene	20	77.6	trace	-
2	3a	H	H	H	1	o-dichlorobenzene	18	6.6	75.6	-
3	3b	H	-(CH ₂) ₂ -	H	1	mesitylene	4	91.2	-	-
4	3c	Et	-(CH ₂) ₂ -	H	1	mesitylene	4	96.4	-	-
5	3d	H	-(CH ₂) ₂ -	H	2	mesitylene	30	56.5	-	-
6	3e	H	-(CH ₂) ₃ -	H	1	mesitylene	15	62.5	11.5	-
7	3f	Et	-(CH ₂) ₃ -	H	1	mesitylene	20	74.5	trace	-
8	3g	H	-(CH ₂) ₄ -	H	1	mesitylene	14	-	21.7	58.3

Cyclization of methyl (*Z*)-isomers (**9a-c**) gave **10a-c** under reflux in mesitylene, but the cyclization reaction was slower than in the case of the corresponding (*E*)-isomers (**3a,b,e**).



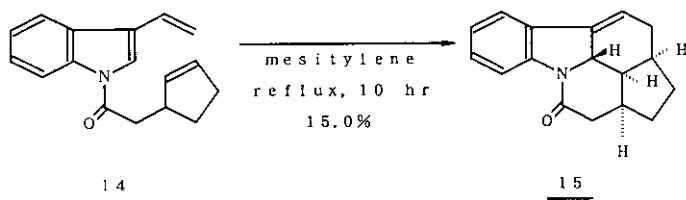
Scheme 3.

Diels-Alder reaction of **12** prepared by alkylation of 3-(1H-indol-3-yl)-2-propenoate (**1a**) with the mesylate (**11**) in DMF gave **13** under reflux in Dowtherm A, but this reaction also did not proceed in mesitylene under reflux.



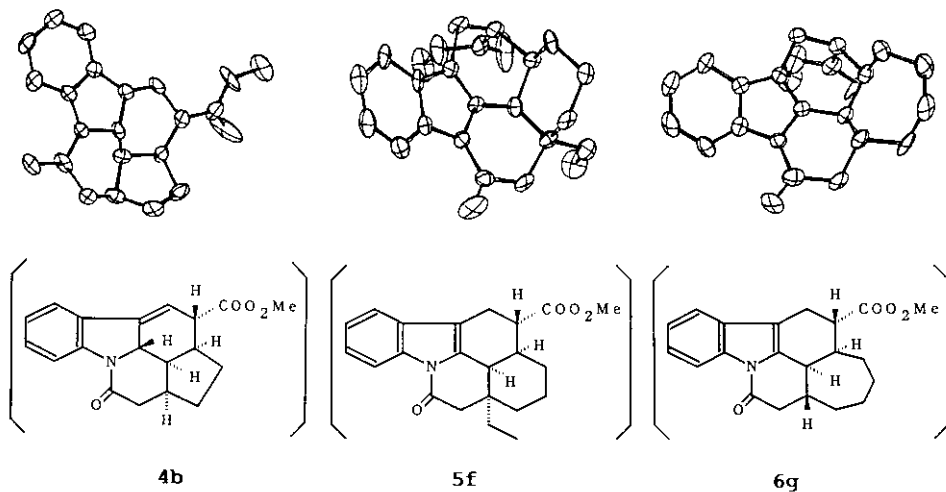
Scheme 4.

Cyclization of **14** required a longer reaction time than the corresponding propenoate (**3b**) and gave the product (**15**) in only 15% yield. Therefore, cyclization of 1-acylated 3-(1H-indol-3-yl)-2-propenoates (**3**) is an inverse electron-demand Diels-Alder reaction.⁵



Scheme 5.

The structures of **4b**, **5f** and **6g** were determined by the X-ray analyses.⁸



In summary, we have developed a new method for stereoselective synthesis of fused indole compounds using intramolecular Diels-Alder reactions. Some of these fused indole compounds showed interesting pharmacological activity such as diuretic activity which will be reported elsewhere.

ACKNOWLEDGEMENTS

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6. All new compounds were characterized by elemental analyses and spectral data. The physical and spectral data are as follows. **4a**: mp 182-184 °C. **4b**: mp 154-156 °C; ir (KBr) 1730 (C=O) and 1665 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 1.35-3.00 (10H, m), 3.80 (3H, s), 3.90 (1H, dt, $J=11, 3$ Hz), 6.13 (1H, t, $J=3$ Hz), 6.94-7.55 (3H, m), 8.03 (1H, d, $J=8$ Hz); ms (m/z) 309 (M^+). **4c**: mp 129-131 °C. **4d**: mp 152-155 °C; ir (KBr) 1740 (C=O) and 1670 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 1.48-2.97 (12H, m), 1.80 (3H, s), 4.30 (1H, dt, $J=11, 3$ Hz), 6.15 (1H, t, $J=3$ Hz), 6.90-7.48 (3H, m), 8.32 (1H, d, $J=8$ Hz); ms (m/z) 323 (M^+). **4e**: mp 172-175 °C; ir (KBr) 1730 (C=O) and 1650 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 1.15-3.00 (9H, m), 3.07 (1H, t, $J=3$ Hz), 3.71 (3H, s), 4.68 (1H, dt, $J=10, 3$ Hz), 5.86 (1H, t, $J=3$ Hz), 6.95-7.53 (3H, m), 8.15 (1H, d, $J=8$ Hz); ms (m/z) 323 (M^+). **4f**: mp 120-122 °C. **5a**: mp 157-159 °C. **5b**: mp 124-126 °C; ir (KBr) 1730 (C=O) and 1700 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 0.80-2.10 (4H, m), 2.37-3.33 (6H, m), 3.72 (3H, s), 7.20-7.55 (3H, m), 8.30-8.50 (1H, m); ms (m/z) 309

(M⁺). **5e**: mp 156-158 °C; ir (KBr) 1730 (C=O) and 1695 (C=O) cm⁻¹; ¹H-nmr (CDCl₃) δ 0.80-1.80 (6H, m), 2.20 (1H, br), 2.40-3.37 (7H, m), 3.80 (1H, s), 7.15-7.50 (3H, m), 8.30-8.60 (1H, m); ms (m/z) 323(M⁺). **5g**: mp 194-196 °C; ir (KBr) 1730 (C=O) and 1695 (C=O) cm⁻¹; ¹H-nmr (CDCl₃) δ 1.22-2.05 (8H, m), 2.38-3.46 (8H, m), 3.68 (3H, s), 7.15-7.58 (3H, m), 8.28-8.52 (1H, m); ms (m/z) 337 (M⁺). **6g**: mp 160-161 °C; ir (KBr) 1722 (C=O) and 1700 (C=O) cm⁻¹; ¹H-nmr (CDCl₃) δ 1.05-2.20 (9H, m), 2.45-3.37 (7H, m), 3.62 (3H, s), 7.15-7.58 (3H, m), 8.25-8.50 (1H, m); ms (m/z) 337 (M⁺). **7**: mp 139-141 °C. **10a**: mp 163.5-165 °C; ir (KBr) 1738 (C=O) and 1645 (C=O) cm⁻¹; ¹H-nmr (CDCl₃) δ 1.55-2.38 (5H, m), 2.50-2.75 (2H, m), 3.57 (1H, m), 3.77 (1H, s), 4.12 (1H, m), 5.87 (1H, t, J=4 Hz), 6.93-7.50 (3H, m), 8.10 (1H, d, J=8 Hz); ms (m/z) 283 (M⁺). **10b**: mp 186-188 °C. **10c**: mp 185-190 °C. **13**: mp 91-92 °C; ir (KBr) 1720 (C=O) cm⁻¹; ¹H-nmr (CDCl₃) δ 0.90-3.10 (11H, m), 3.30 (1H, t, J=8 Hz), 3.70 (3H, s), 3.60-4.20 (2H, m), 6.95-7.34 (3H, m), 7.38-7.60 (1H, m); ms (m/z) 295 (M⁺). **15**: mp 157-159 °C; ir (KBr) 1670 (C=O) cm⁻¹; ¹H-nmr (CDCl₃) δ 1.03-3.05 (10H, m), 3.98 (1H, ddd, J=11, 4, 4 Hz), 6.02 (1H, m), 6.93-7.54 (3H, m), 8.11 (1H, d, J=8 Hz); ms (m/z) 251 (M⁺).

7. The transformation from **4b** to **5b** was performed in the presence of catalysts as follows:

- 1) Wilkinson's catalyst in xylene under reflux, 88.6% yield;
- 2) 10% Pd on C in xylene under reflux, 98% yield;
- 3) 5% Rh on C in xylene under reflux, 32% yield;
- 4) HCl in methanol under reflux, 100% yield.

8. Crystal data of **4b**: C₁₉H₁₉NO₃=309.4, monoclinic, P2₁/c, a=13.860(6), b=6.935(7), c=16.841(5) Å, β=111.38(3)°, U=1507.5 Å³, Z=4, D_c=1.36 g.cm⁻³, R=0.083; **5f**: C₂₂H₂₅NO₃=351.4, monoclinic, p2₁/a, a=8.781(2), b=21.886(6), c=9.680(2) Å, β=74.662(2)°, U=1790.4 Å³, Z=4, D_c=1.30 g.cm⁻³, R=0.097; **6g**: C₂₁H₂₃NO₃=337.4, monoclinic, p2₁/n, a=8.020(1), b=17.311(3), c=12.510(1) Å, β=98.16(1)°, U=1719.4 Å³, Z=4, D_c=1.30 g.cm⁻³, R=0.067.

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