

A novel intramolecular Diels–Alder cyclization involving indoloazepines

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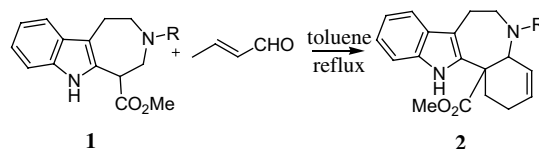
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Abstract—The reaction of indoloazepines **1** and α,β -unsaturated aldehydes in reflux toluene led to tetracyclic compounds **2**. The key to this reaction was an intramolecular Diels–Alder cycloaddition by the indoloacrylate (dienophile)–dienamine (diene) intermediates generated in situ.

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The intramolecular Diels–Alder reaction is a powerful tool in the construction of fused ring systems with one six-membered ring and has been widely used in total syntheses of polycyclic natural products.¹ In a series of papers,² Kuehne and co-workers described the syntheses of the core structure of aspidosperma alkaloids and binary alkaloids (e.g., Fig. 1) based on the intramolecular Diels–Alder reaction of indoloacrylate (diene)–enamine (dienophile) intermediates. Herein, we report a novel intramolecular Diels–Alder reaction based on the reaction of indoloazepines and α,β -unsaturated aldehydes.

This investigation was based on a reaction result in the attempt to prepare andranginine.³ As shown in Scheme 1, indoloazepine **1** (R = Bn) was reacted with crotonaldehyde in refluxing toluene to yield tetracyclic compound **2a** (R = Bn) in 83% yield.⁴ Further study was conducted by varying the *N*-substituents and α,β -unsaturated aldehydes. The results are listed in Table 1. The reported structures in Table 1 were the sole isomers detected and isolated from the reactions. All the products



Scheme 1.

were characterized by NMR spectra, MS, and elemental analysis. In addition, product **2a** (R = Bn) was determined by an X-ray crystallographic experiment (Fig. 2). The X-ray structure revealed an *anti* relationship between the carbomethoxy group and the proton atom at the neighboring tertiary carbon.

As expected, indoloazepine **1** with *N*-substituent (R = Bn, Allyl, Et, and *n*-Bu), prepared according to a literature procedure,⁵ was reacted with crotonaldehyde to give tetracyclic compounds **2** in moderate to good yield (Table 1, entry 1–4). While aldehydes with electron-donating β -substituents resulted in the expected tetracycles **2** (entry 5 and 8) in good chemical yields, α,β -unsaturated aldehydes with α -substituent (entry 6) or β -phenyl (entry 7) gave lower yields. In fact, the reaction of *N*-benzylindoloazepine **1** with α -methylpent-2-enal was very slow and a large amount of starting materials were still left after being refluxed for 4 days in toluene. In order to accelerate the reaction, catalysts such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$, ZnCl_2 , CF_3COOH , Et_3N , and DBU were screened in heated sealed tubes with indoloazepine **1** and α -methylpent-2-enal in toluene. In all these cases, complex materials with only trace amount of the desired

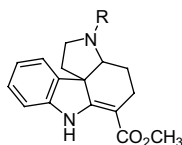
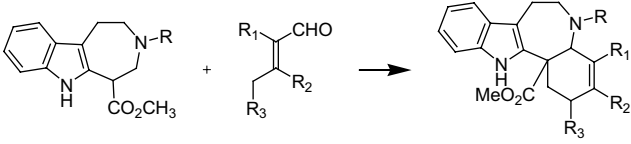
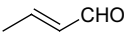
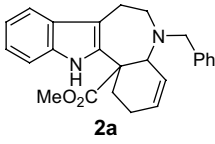
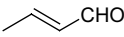
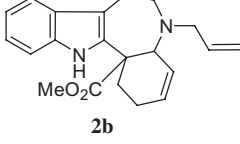
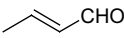
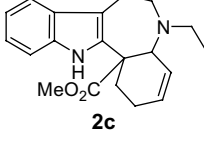
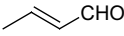
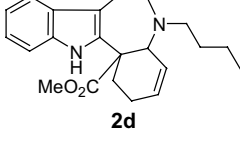
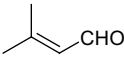
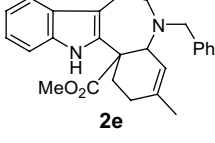
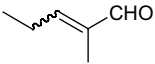
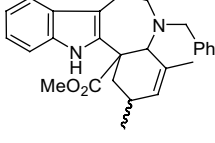
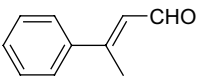
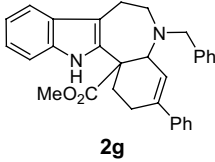
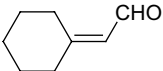
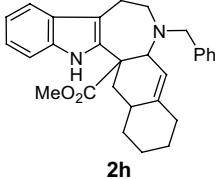


Figure 1.

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Table 1.

					
Entry	R	α,β -Unsaturated aldehydes	Product	Time (h)	Yield (%)
1	Bn		 2a	Overnight	83
2	Allyl		 2b	6	87
3	Et		 2c	6	57
4	<i>n</i> -Bu		 2d	7	48
5	Bn		 2e	3	89
6	Bn		 2f (isomeric ratio 1:3)	8 ^a	52
7	Bn		 2g	5	65
8	Bn		 2h	2	92

^a The reaction was conducted in refluxing xylene with catalytic amount of benzoic acid.

product were detected by LC–MS. It was found that the reaction was facilitated by catalytic amount of benzoic acid in refluxing xylene to yield two diastereomeric isomers in 13% and 39%, respectively.⁶

The above results might be explained by tandem reaction paths via an intramolecular Diels–Alder cyclization of key intermediate **4** similar to the one proposed for catharanthine biosynthesis⁷ as depicted in Scheme 2.

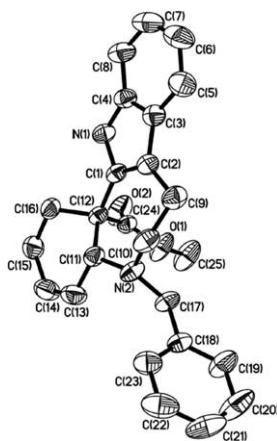
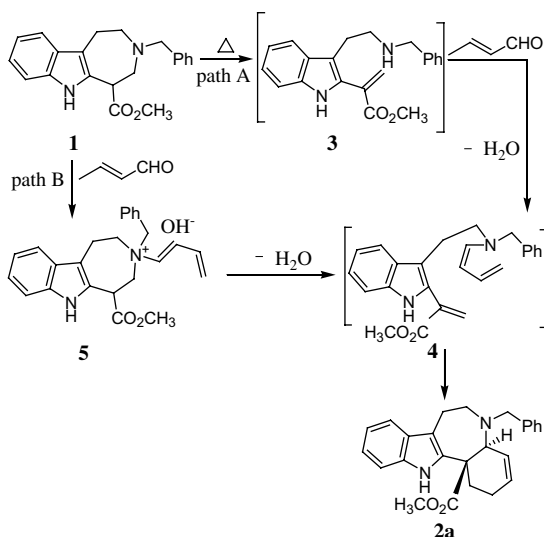


Figure 2. X-ray structure of cycloadduct **2a**.



Scheme 2.

N-Benzyl-indoloazepine **1** might undergo thermal elimination to give an indoloacrylate secondary amine **3**,^{2c} which could be condensed with an α,β -unsaturated aldehyde such as crotonaldehyde to yield indoloacrylate-dienamine **4** (path A). Subsequently, intermediate **4** could undergo an intramolecular Diels–Alder *endo* cycloaddition to give tetracyclic product **2**. Alternatively, in path B, indoloacrylate **1** could be condensed with an aldehyde to form quaternary salt **5**. Salt **5** could undergo β -elimination and lose a molecule of water to yield the key Diels–Alder intermediate **4**. The proposed mechanism was consistent with the reaction results listed in Table 1. In the case of entry 6, the α -substituent of butenal hindered its condensation with either elimination product **3** in path A or indoloazepine **1** in path B to make the overall reaction sequence difficult to proceed.

In conclusion, a novel intramolecular Diels–Alder cycloaddition by the indoloacrylate (dienophile)–dienamine (diene) intermediates, generated in situ by the reaction of indoloazepines and α,β -unsaturated aldehydes, has

been developed. This reaction can provide a convenient access to complex tetracyclic structures.

Acknowledgments

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- This work was based on the initial result from one of the authors Wang, T.
- A typical procedure was as follows: A mixture of *N*-benzylindoloazepine **1** (334 mg, 1 mmol) and crotonaldehyde (70 mg, 10 mmol) in toluene (10 mL) was refluxed with stirring overnight under nitrogen atmosphere. After removal of the solvent in vacuo, the crude product was purified by flash chromatography on silica gel eluting with petroleum ether/EtOAc (10/1, v/v) to yield product **2a** 322 mg (83%), white solid, mp 172–173 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.14 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.40–7.33 (m, 5H), 7.27–7.24 (m, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 5.91–5.89 (m, 1H), 5.83 (d, *J* = 10.5 Hz, 1H), 4.58 (s, 1H), 4.35 (d, *J* = 15.5 Hz, 1H), 3.80 (d, *J* = 15.5 Hz, 1H), 3.68 (s, 3H), 3.18–3.14 (m, 2H), 3.10–3.07 (m, 1H), 2.92–2.88 (m, 1H), 2.58–2.56 (m, 1H), 2.55–2.45 (m, 1H), 2.23–2.19 (m, 1H), 2.13–2.07 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 173.36, 142.01, 136.77, 134.98, 129.65, 128.43, 128.02, 127.90, 126.70, 122.04, 119.51, 118.52, 114.70, 110.77, 64.43, 53.52, 52.40, 52.36, 51.03, 32.47, 23.31, 22.16; Anal. Calcd for C₂₅H₂₆N₂O₂ (386.20): C, 77.69; H, 6.78; N, 7.25. Found: C, 77.78; H, 6.85; N, 7.34.
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- Preparation of products **2f**: A solution of the *N*-benzylindoloazepine **1** (668 mg, 2 mmol), 2-methylpent-2-enal (980 mg, 10 mmol), and a catalytic amount of benzoic acid in xylene (20 mL) was refluxed for 8 h under nitrogen (TLC showed complete consumption of the indoloazepine). The solvent was removed in vacuo. The resulted dark red residue was dissolved in 50 mL EtOAc, washed with saturated NaHCO₃ and brine in sequence, dried over anhydrous Na₂SO₄, concentrated in vacuo, followed by flash chromatography on silica gel eluting with petroleum ether/EtOAc (25:1, v/v) to give two diastereomeric isomers: minor isomer (less polar): 108 mg (13%), mp 166–167 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.24 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.32–7.29 (m, 5H), 7.23 (m, 1H), 7.19 (t,

$J = 7.5$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 5.54 (s, 1H), 4.53 (s, 1H), 4.06 (d, $J = 13.5$ Hz, 1H), 3.97 (d, $J = 13.5$ Hz, 1H), 3.72 (s, 3H), 3.32–3.30 (m, 1H), 3.18 (d, $J = 9.0$ Hz, 2H), 2.93–2.91 (m, 1H), 2.62–2.58 (m, 1H), 2.48 (br s, 1H), 1.98 (s, 3H), 1.82 (t, $J = 13.5$ Hz, 1H), 1.02 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 174.60, 140.82, 135.42, 133.78, 133.0, 131.43, 128.96, 128.40, 128.33, 126.75, 122.24, 119.28, 118.65, 111.88, 110.49, 64.37, 56.27, 52.77, 51.70, 51.33, 38.48, 29.10, 23.29, 22.64, 21.32; Anal. Calcd for $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_2$ (414.54): C, 78.23; H, 7.29; N, 6.76. Found: C, 78.20; H, 7.45; N, 6.77; major isomer: 321 mg (38%), mp 116–117 °C. ^1H NMR (500 MHz, CDCl_3): δ 8.36 (s, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 7.5$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.22 (d,

$J = 7.0$ Hz, 1H), 7.19 (t, $J = 7.0$ Hz, 1H), 7.10 (t, $J = 7.0$ Hz, 1H), 5.53 (s, 1H), 4.43 (d, $J = 16.0$ Hz, 1H), 4.34 (s, 1H), 3.89 (d, $J = 15.5$ Hz, 1H), 3.61 (s, 3H), 3.24–3.22 (m, 1H), 3.15–3.09 (m, 2H), 2.82–2.79 (m, 1H), 2.55–2.52 (m, 2H), 2.45–2.41 (m, 1H), 1.99 (s, 3H), 1.25 (t, $J = 7.0$ Hz, 1H), 1.07 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 174.14, 140.84, 136.24, 135.24, 128.42, 128.33, 128.15, 127.99, 126.46, 122.18, 119.35, 118.65, 113.78, 110.66, 68.37, 58.68, 51.93, 50.41, 42.19, 28.87, 22.31, 21.89, 20.79, 18.63; Anal. Calcd for $\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_2$ (414.23): C, 78.23; H, 7.29; N, 6.76. Found: C, 78.15; H, 7.20; N, 6.59.

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