



Pergamon

Tetrahedron Letters 41 (2000) 4657–4661

TETRAHEDRON  
LETTERS

## A new Claisen sequence for the synthesis of 3-substituted-2-oxindoles

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Received 9 March 2000; accepted 20 April 2000

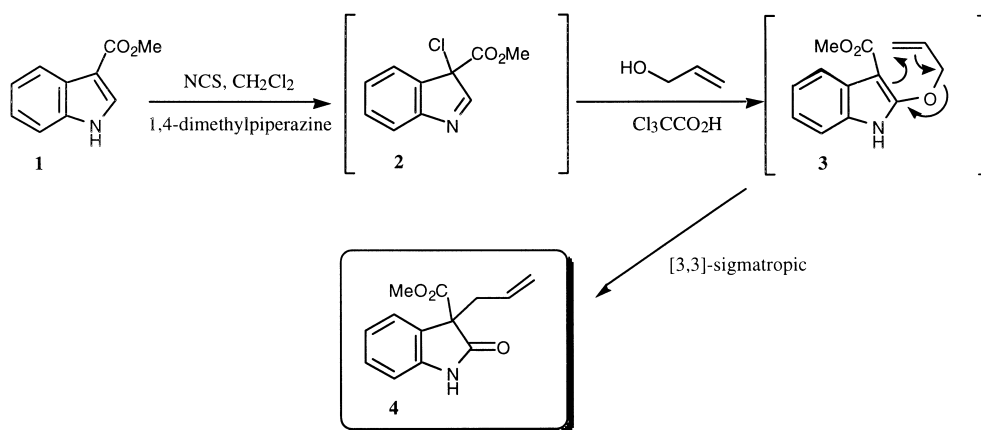
### Abstract

Treatment of 3-methoxycarbonylindole with *N*-chlorosuccinimide followed by a range of alkenols yields 3-allylated-2-oxindoles in good yield, via a novel addition–Claisen rearrangement sequence. © 2000 Elsevier Science Ltd. All rights reserved.

Recently, as part of a drug development programme, the 2-propenyloxyindole-3-carboxylic acid derivative **3** was required in multigram quantities. Following a well-established in-house procedure for the synthesis of 2-alkoxy indoles<sup>1</sup> the methyl ester **1** was treated with NCS followed by allyl alcohol in the presence of an acid catalyst. To our surprise, the only product isolated was the 3-allylated oxindole derivative **4** in excellent yield. The formation of **4** can be rationalised by considering the sequence outlined in Scheme 1. Thus, reaction of the indole **1** with NCS in the presence of 1,4-dimethylpiperazine gives the highly reactive chloroindolenine **2**, which, upon treatment with allyl alcohol under acidic conditions, gives rise to the desired product **3**. We believe, however, that under the reaction conditions this undergoes a rapid [3,3] sigmatropic rearrangement (Claisen) to give the oxindole **4**.<sup>2</sup> In this letter we report the scope and limitations of this tandem process with respect to the allylic alcohol partner.

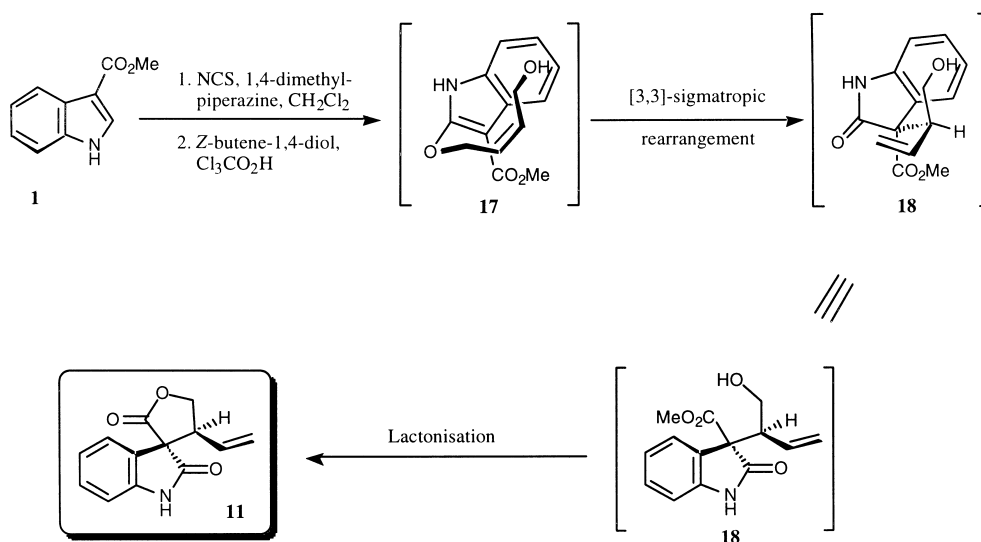
Initially, we concentrated on the methyl indole 3-carboxylic ester **1** and soon found that this reaction sequence was general for a variety of primary and secondary alkenols (Table 1)—tertiary alcohols fail to react for steric reasons. In general, the reaction of in situ-generated **2** with the alkenol partners involved was rapid and the 2-propenyloxyindole products were formed within 1 h of the addition of the alkenol (entries 1–11). Rearrangement to the oxindole products **4–16** proceeded efficiently on standing, and although the reaction times varied from about 10 min to several days, the slower examples could be accelerated by heating. The reaction proved to be very tolerant of methyl substitution on all positions of the alkenol unit (entries 2–5), even when the

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Scheme 1.

rearranged product contained two adjacent quaternary carbon centres (entry 5). In the case of *Z* alkenols the rearrangement proved to be highly stereoselective and yielded the oxindoles as single diastereomers (entries 7 and 8) where the relative stereochemistry was entirely consistent with the generally accepted mechanism for the Claisen rearrangement (*vide infra*). With *E* alkenols the reaction gave the products as mixtures of diastereomers (entries 4 and 6) presumably due to an unfavourable steric interaction of the methyl ester with the *E* substituent forcing the adoption of a boat-like transition state. In the case of propargyl alcohols (entries 12 and 13) the sequence provided a very efficient route to the corresponding allene-oxindoles **15** and **16**. The use of *cis*-2-butene-1,4-diol (entry 8) gave rise to the very interesting spiro oxindole-lactone **11** as a single diastereoisomer in excellent overall yield.<sup>4</sup> The reaction proceeds via Claisen rearrangement of the indole **17** to give the hydroxy ester **18** which then undergoes spontaneous lactonisation to **11**. The stereochemistry of this and most other examples can be rationalised on the basis that **17** undergoes rearrangement in the chair form as shown in Scheme 2.



Scheme 2.

Table 1  
Synthesis 3,3-difunctionalised oxindoles<sup>3</sup>


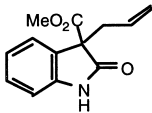
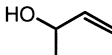
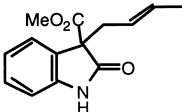
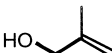
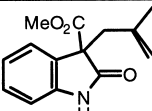

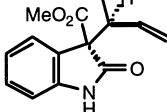
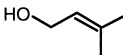
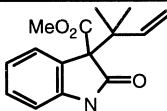

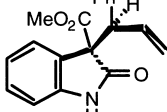
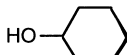
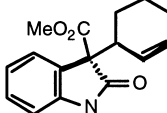

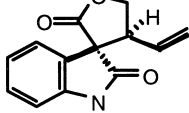
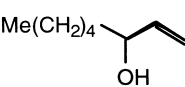
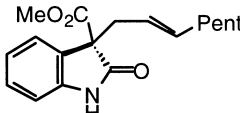
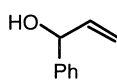
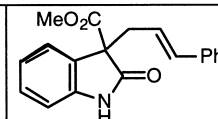
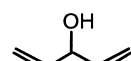
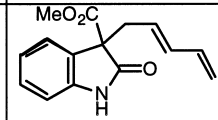
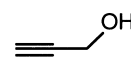
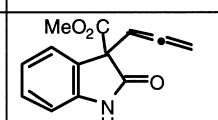

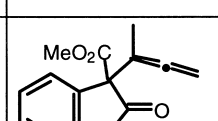
Entry	Alkenol	Product	Time	Yield	
1			4	48hr at RT	91%
2			5 exclusively <i>E</i>	5hr at RT	69%
3			6	4 days at RT	96%
4			7 1:2.9 mixture of diastereomers	3hr at RT	94%
5			8	1hr at RT	89%
6			9 1:1.64 mixture of diastereomers	18hr at RT	55%
7			10 single diastereomer	36hr at RT	61%
8			11 single diastereomer	1hr at RT	79%
9			12 exclusively <i>E</i>	48hr	53%

Table 1 (continued)

10			<b>13</b> exclusively <i>E</i>	2hr	54%
11			<b>14</b> exclusively <i>E</i>	<1hr	74%
12			<b>15</b>	10min at reflux	97%
13			<b>16</b>	10min at reflux	93%

In summary, a new method for the formation of 3,3-disubstituted-2-oxindoles has been described which involves a novel addition–Claisen rearrangement sequence of 3-methoxy-carbonylindole. The reaction is general for a variety of alkenols and alkynols and is amenable to scale up. Current work is involved with the evaluation of this sequence in alkaloid synthesis.

### Acknowledgements

The authors would like to thank Tony Beck, SmithKline Beecham Pharmaceuticals, for help with running and interpreting NMR spectra.

### References

- (a) Fedouloff, M.; Strachan, J. B. (SmithKline Beecham plc, UK) Patent WO 99-EP4944 19990713. (b) Fedouloff, M.; Strachan, J. B. (SmithKline Beecham plc, UK) Patent WO 99-EP4943 19990713.
- For specific indole Claisen rearrangements, see: (a) Somei, M.; Yamada, F.; Fukui, Y.; Shinmyo, D. *Heterocycles* 1993, **35**, 99. (b) Somei, M.; Yamada, F.; Izumi, T.; Nakajou, M. *Heterocycles* 1997, **45**, 2327. (c) Sakamoto, M.; Kawasaki, T.; Tarashima, R.; Sakaguchi, K.; Sekiguchi, H. *Tetrahedron Lett.* 1996, **37**, 7525. (d) Merour, J.-Y.; Malapel-Andrieu, B.; Piroelle, S. *J. Chem. Res. (S)* **1998**, 594.
- Typical experimental procedure for methyl 2,3-dihydro-2-oxo-3-(2-propenyl)-1H-indole-3-carboxylate **4**: A suspension of methyl indole-3-carboxylate (20.0 g, 114.3 mmol) in dichloromethane (100 ml) was cooled to 0°C under nitrogen and treated sequentially with dimethylpiperazine (4.30 g, 64.0 mmol) and *N*-chlorosuccinimide (16.8 g, 125.6 mmol) in one portion. The resulting solution was stirred for 2 h at 0°C and then added to a solution of allyl alcohol (13.3 g, 17.7 ml, 228.6 mmol) and trichloroacetic acid (4.48 g, 27.4 mmol) in dichloromethane (100 ml) maintaining the temperature below 25°C. After 2 h the reaction mixture was washed twice with 10% aqueous sodium bicarbonate solution then with 0.5 M aqueous hydrochloric acid and finally with water. The resulting solution was dried, filtered, evaporated to dryness and the residue redissolved in toluene. After stirring for 48 h in the presence of silica gel at ambient temperature the product was isolated by column chromatography (silica gel,

40% ethyl acetate/hexane) giving the title product **4** as a white solid (23.98 g, 91% yield). A portion was recrystallised from ethyl acetate and hexane. Mp 130–132°C;  $^1\text{H}$  (CDCl<sub>3</sub>)  $\delta_{\text{H}}$  9.14 (s, 1H, NH), 7.26 (m, 2H, C(4,6)H), 7.06 (td, 1H,  $J=7$ , 1 Hz, C(5)H), 6.94 (dd, 1H,  $J=8$ , 1 Hz, C(7)H), 5.44 (m, 1H, C(13)H), 5.06 (dd, 1H,  $J=17$ , 2 Hz, C(14)H), 4.96 (dt, 1H,  $J=10$ , 1 Hz, C(14')H), 3.69 (s, 3H, ester), 3.03 (dd, 1H,  $J=14$ , 7 Hz C(12)H), 2.98 (dd, 1H,  $J=14$ , 7 Hz, C(12')H);  $^{13}\text{C}$  (CDCl<sub>3</sub>)  $\delta_{\text{C}}$  176.2 (C 10), 169.4 (C 2), 141.4 (C 8), 130.8 (C(6)H), 129.1 (C(13)H), 128.1 (C 9), 124.0 (C(4)H), 122.8 (C(5)H), 120.0 (C(14)H<sub>2</sub>), 110.3 (C(7)H), 59.7 (C 3), 53.1 (OCH<sub>3</sub>), 38.5 (C(12)H); IR  $\nu_{\text{max}}$  3164 (m, N–H), 2923 and 2853 (s, N), 1741 (s, C=O ester), 1726 (s, C=O amide), 1682 (m), 1620 (w), 1474 (m, N), 1464 (m, N), 1377 (m), 1238 (s, asym C–O–C), 746 (w, CH(4H)) cm<sup>-1</sup>;  $m/z$  (EI)  $m^+$  231 (72%), 199 (10%), 190 (100%), 172 (42%), 162 (60%), 144 (17%), 132 (14%), 119 (15%). C<sub>13</sub>H<sub>13</sub>NO<sub>3</sub> requires: 231.0895. Found: 231.0901. Analysis calculated for C<sub>13</sub>H<sub>13</sub>NO<sub>3</sub>: C, 67.50%; H, 5.66%; N, 6.06%. Found: C, 67.49%; H, 5.60%; N, 5.99%.

4. For example, cycloadduct **11** exhibited the following NOE enhancements:

