SYNTHESIS OF 1,2-DIHYDRO-2-ALLYLINDOL-3-ONES USING *IN SITU* CLAISEN REARRANGEMENT OF 1,2-DIHYDROINDOL-3-ONES WITH ALLYL ALCOHOLS

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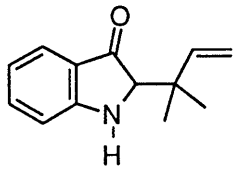
Thermal treatment of 1,2-dihydroindol-3-ones (**2**) with allyl alcohols (**3**) in the presence of camphorsulfonic acid and magnesium sulfate advances a sequence of condensation and Claisen rearrangement to give 1,2-dihydro-2-allylindol-3-ones (**6**) including 2-(1,1-dimethylallyl) derivatives (**1**).

KEYWORDS 1,2-dihydro-2-allyl-indol-3-one; Claisen rearrangement; condensation; indol-3-one; allyl alcohol

1,2-Dihydroindol-3-ones are key intermediates in the synthesis of alkaloids and biologically active compounds.[1] 2-(1,1-Dimethylallyl)indol-3-one (**1**) is of particular interest for synthesizing alkaloids containing a 1,1-dimethylallyl group at the 2-position of the indole nucleus, such as austamide,[2] brevianamides,[3,4] neoechinuline,[5] and others.[6] Although several efficient methods for the synthesis of 1,2-dihydroindol-3-ones have been reported recently,[7] 1,2-dihydro-2-(1,1-dimethylallyl)-indol-3-one (**1**) is still difficult to obtain.



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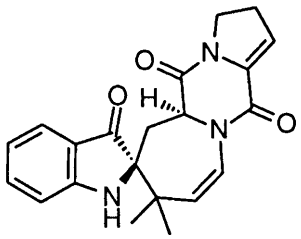
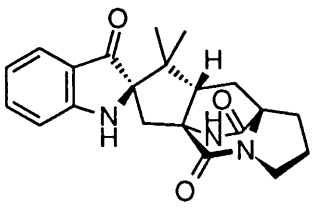
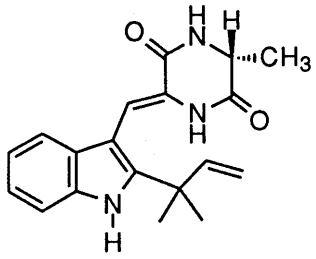


austamide



brevianamide A



neoechinulin A

Claisen rearrangement of 3-allyloxyindole (**4**) seems to be an attractive process for introducing an allyl group into the indole 2-position; however, the preparation of 3-allyloxyindole (**4**) is difficult.[8] We describe here the easy synthesis of 1,2-dihydro-2-(1,1-dimethylallyl)indol-3-ones (**1**) and the related derivatives (**6**) using a Claisen rearrangement of 3-allyloxyindoles (**4**) generated by a direct condensation of 1,2-dihydroindol-3-ones (**2**) with allyl alcohol (**3**).

The starting 1,2-dihydroindol-3-ones (**2**) were readily available by our previously described method.[9] Initially, 1-acetyl-1,2-dihydroindol-3-one (**2a**) was treated with 3,3-dimethylallyl alcohol (**3a**) in the presence of catalytic *p*-toluenesulfonic acid and magnesium sulfate[10] at 130 °C to give the

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This paper is dedicated to Professor Yasumitu Tamura on the occasion of his 70th birthday.

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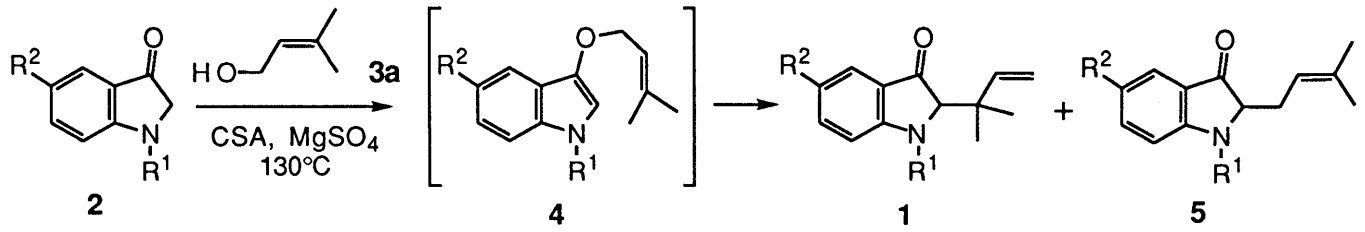


Table I. Preparation of Indol-3-ones (**1**) and (**5**)[a]

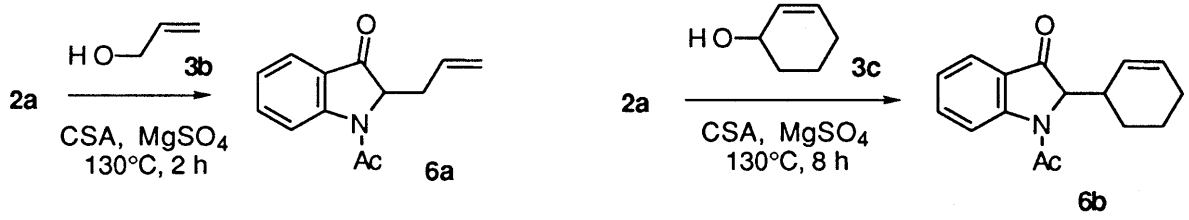
				Reaction conditions			Yield (%)[b]	
Entry	2	R^1	R^2	Acid	Temp. (°C)	Time (h)	1	5
1	a	Ac	H	TsOH	130	6	37	18
2	a	Ac	H	TsOH	180	3	32	26
3	a	Ac	H	CSA	130	3	62	11
4	b	Ac	OMe	CSA	130	7	66	11
5	c	Ac	Br	CSA	130	6.5	37	19
6	d	COPh	H	CSA	130	4	59	13
7	e	CO_2Me	H	CSA	130	10	66	trace

a) All new compounds gave satisfactory spectroscopic and analytical data. b) Isolated yield.

desired Claisen product, 1-acetyl-1,2-dihydro-2-(1,1-dimethylallyl)indol-3-one (**1a**) in 37% yield, together with the isomeric 3,3-dimethylallyl derivative (**5a**) (18%) (Table I, Entry 1). A higher reaction temperature resulted in a reduction in the proportion of Claisen product (**1a**) obtained (Entries 1 and 2). When the reaction was performed using camphorsulfonic acid (CSA) instead of *p*-toluenesulfonic acid , the yield of **1a** was improved (62%), though it was still accompanied by the formation of **5a** (11%) (Entry 3).[11] Similarly, the CSA-promoted reaction of the indol-3-ones (**2b-d**) with 3,3-dimethylallyl alcohol (**3a**) afforded the corresponding **1b-d** as major products, along with **5b-d**, respectively (Table I, Entries 4-6). The reaction of a 1-methoxycarbonyl derivative (**2e**) required prolonged heating, but the desired [3,3] product (**1e**) was preferentially obtained in good yield (Entry 7).

The difference between the ratio of products (**1a**) and (**5a**) (5.5 : 1) in the reaction using CSA (Entry 3) and that (2 : 1) using *p*-toluenesulfonic acid (Entry 1) indicates that these acids participate not only in the initial condensation step but also in the Claisen rearrangement step.

In order to explore the applicability of this *in situ* Claisen rearrangement, we also examined the reaction of **2a** with allyl alcohols (**3b** and **3c**). These reactions proceeded more smoothly under the same conditions to give the corresponding 2-allyl-1,2-dihydroindol-3-ones (**6a**) (73%) and (**6b**) (67%), respectively. Further scope and limitation are now under investigation.



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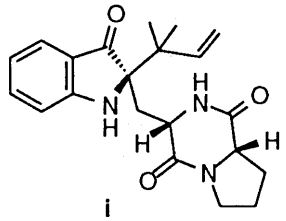

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10) The reaction was slow unless magnesium sulfate was added.

11) A mixture of **2a** (0.17 mmol), **3a** (9.8 mmol), CSA (0.015 mmol), and magnesium sulfate (75 mg) was heated in a sealed tube at 130 °C with stirring for 3 h. After removal of the magnesium sulfate, the solution was concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel with diethyl ether-hexane (2 : 1) as an eluent to give **1a** (62%) and **5a** [7a] (11%). **1a**; HRMS *m/z* Calcd. for $C_{15}H_{17}NO_2$ 243.1259, Found 243.1261; $\nu_{max}(CHCl_3)/cm^{-1}$ 1721 and 1678; δ_H(270MHz; $CDCl_3$) 0.96 (3H, s),1.12 (3H, s), 2.33 (3H, s), 4.32 (1H, br s), 4.89 (1H, d, J=8.9 Hz), 4.90 (1H, d, J=18.8 Hz), 5.75 (1H, ddd, J=17.5, 10.6, and 1.6 Hz), 7.15 (1H, t, J=9.6 Hz), 7.53-7.60 (2H, m), and 7.81 (1H, br s).

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