Brønsted Acid Catalysed Electrophilic Substitution of Indole by Allylic Alcohols in Lithium Perchlorate–Diethyl Ether: Application to the Total Synthesis of Yuehchukene

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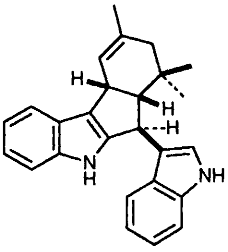
A novel carbon–carbon bond-forming reaction between indole and β,β-disubstituted allylic alcohols in lithium perchlorate–diethyl ether containing a catalytic amount of a Brønsted acid is described; the reaction has been applied to a total synthesis of yuehchukene.

We recently demonstrated the utility of the unusual solvent system 3.0 mol dm^{-3} lithium perchlorate in diethyl ether for activating β,β-disubstituted allylic alcohols toward direct substitution by 1-methoxy-1-(*tert*-butyldimethylsiloxy)-ethene.[1] We report here that β,β-disubstituted allylic alcohols undergo reaction with indole in lithium perchlorate–diethyl ether containing a catalytic amount of Brønsted acid. This novel carbon–carbon bond-forming reaction has been applied to a total synthesis of yuehchukene **1**.

Preliminary experiments demonstrated that no reaction was observed upon exposure of a 0.1 mol dm^{-3} solution of isophorol **2** in freshly prepared 3.0 mol dm^{-3} lithium perchlorate–diethyl ether to 2.0 equiv. of freshly sublimed indole. However, addition of 0.01 equiv. of acetic acid[2] to the above reaction resulted in rapid consumption of starting material, giving rise (30 min) to the indole substitution product **3** in 77% yield (Scheme 1). Approximately 6% of the isomeric, allylically transposed product was isolated. Similar results have been observed with other β,β-disubstituted allylic alcohols (Table 1).

Particularly noteworthy in Table 1 are entries 3 and 4 wherein the triisopropylsilyl and thioenol ethers survive the reaction conditions and do not promote cyclohexenone formation.[3] In general, reactions are complete within 30 min. Attempts to employ 1.0 mol dm^{-3} lithium perchlorate–diethyl ether containing 0.01 equiv. of acetic acid as the reaction medium resulted in increased reaction times, lower yield of substitution products, and formation of byproducts. *E.g.* the



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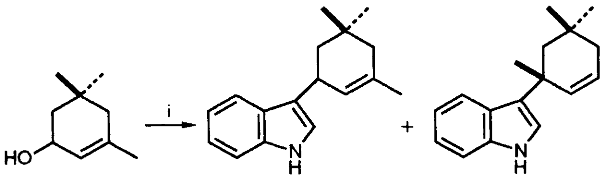
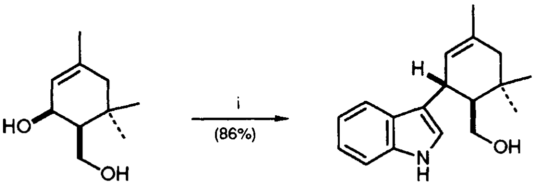


2 **3** minor product

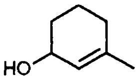
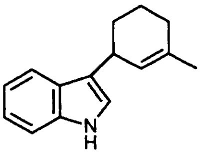
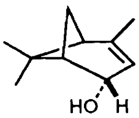
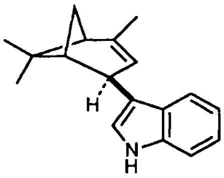
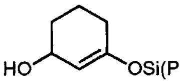
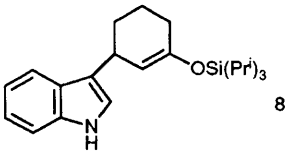
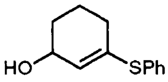
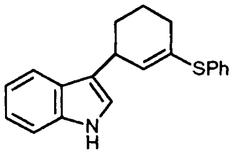
Scheme 1 *Reagents*: i, $LiClO_4$–Et_2O (3 mol dm^{-3}), HOAc (0.01 equiv.), indole (2.0 equiv.)



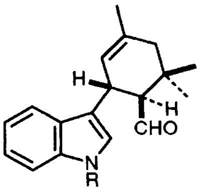
4 **5**

Scheme 2 *Reagents*: i, $LiClO_4$–Et_2O (1 mol dm^{-3}), HOAc (0.01 equiv.) indole (2.0 equiv.)

Table 1 Acetic acid catalysed electrophilic substitution of indole by allylic alcohols in lithium perchlorate–diethyl ether[a]

Entry	Substrate	Product	Yield (%)[b]
1			82[c]
2			90[c]
3			81
4			97

[a] All reactions were conducted at ambient temperature employing a 0.1 mol dm^{-3} solution of substrate in 3.0 mol dm^{-3} $LiClO_4$–Et_2O containing 0.01 equiv. of HOAc and 2.0 equiv. of indole and were complete in 30 min. [b] Isolated yields. [c] Approximately 5% of the allylically transposed isomer was isolated.



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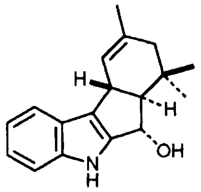

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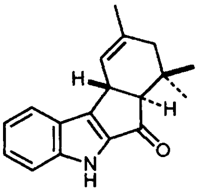

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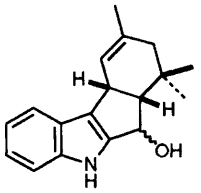

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reaction of isophorol with 2.0 equiv. of indole in 1.0 mol dm^{-3} lithium perchlorate–diethyl ether containing 0.01 equiv. of acetic acid was complete after 1.5 h giving rise to only a 56% yield of **3** along with a considerable amount of diene formation. A requirement for carbon–carbon bond formation is that the allylic alcohol be secondary and possess β,β-disubstitution. Attempts to carry out the above reaction with cyclohexenol lead exclusively to recovered starting material.

In order to demonstrate the potential of this novel carbon–carbon bond-forming reaction we applied the above methodology to a total synthesis of the unique bis-indole alkaloid yuehchukene **1**.[4] Isolated[5] from the roots of Yueh-Chu, *Murraya paniculata* (*L*) Jack, in racemic form, yuehchukene possesses potent anti-implantation activity in rats.

The synthesis of **1** commences with crystalline allylic diol **4**, readily available in *ca.* 50% overall yield from isophorone by methoxycarbonylation of the kinetic enolate with methyl cyanoformate followed by sequential reduction of the β-keto ester with sodium borohydride in methanol and lithium aluminium hydride in diethyl ether. Treatment of a 0.1 mol dm^{-3} solution of **4** with 1.0 mol dm^{-3} lithium perchlorate–diethyl ether containing 0.01 equiv. of acetic acid : 2.0 equiv. of indole gave **5** after 1.5 h at ambient temperature in 86% yield (Scheme 2). Approximately 5% of the allylically transposed indole was isolated. No reaction was observed in the absence of lithium perchlorate.

Standard oxidation methods failed to oxidise the primary alcohol **5** to the corresponding aldehyde; however, treatment of **5** with an excess of *tert*-butoxymagnesium bromide in tetrahydrofuran (THF) followed by the addition of 1,1′-(azodicarbonyl)dipiperidine[6] afforded after 1 h at ambient temperature an 81% yield of aldehyde **6** (R = H). Benzoylation [BzCl (Bz = benzoyl), Et_3N, 4-dimethylaminopyridine, $ClCH_2CH_2Cl$, 75 °C, 2 h] of the indole nitrogen gave rise (88%) to **6** (R = Bz), thus allowing deprotonation at C(2) on the indole ring. Treatment of **6** (R = Bz) with 6.0 equiv. of lithium diisopropylamide in THF at −78 °C provided a 65% yield of tetracyclic alcohol **7** in addition to *ca.* 16% of debenzoylated starting material **6** (R = H). Note that in the formation of **7**, the C(2) position of the indole is preferentially deprotonated since the rotamer required for proton abstraction adjacent to the aldehyde is not accessible.

Oxidation of the alkoxymagnesium bromide derived from **7** with 1,1′-(azodicarbonyl)dipiperidine in THF at 55 °C for 30 min gave rise to the *trans*-fused ketone **8** in 80% yield. Epimerization of **8** to the *cis*-fused ketone followed by reduction employing the Kutney protocol[4d] afforded **9** as a 2 : 1 mixture of diastereoisomers. Treatment (30 min) of a 0.1 mol dm^{-3} solution of the major isomer of **9** (α-OH) in 3.0 mol dm^{-3} lithium perchlorate–diethyl ether with 2.0 equiv. of indole in the absence of added Brønsted acid gave rise to yuehchukene in 97% yield as an amorphous solid m.p. 128 °C (lit.[5] m.p. 127 °C). The spectra data for **1** (IR, ^1H NMR, UV, mass) were identical to the data reported in the literature for natural yuehchukene. The reaction of **9** (β-OH) in lithium perchlorate–diethyl ether with indole under identical conditions proceeded at a much slower rate, giving rise after 3 h to an 86% yield of yuehchukene.

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