

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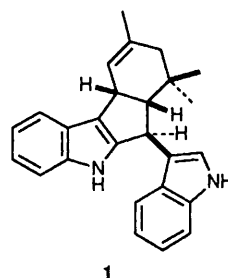
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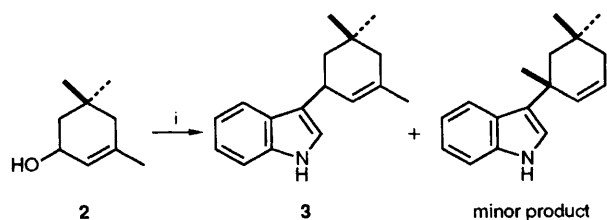
A novel carbon–carbon bond-forming reaction between indole and β,β -disubstituted allylic alcohols in lithium perchlorate–diethyl ether containing a catalytic amount of a Brønsted acid is described; the reaction has been applied to a total synthesis of yuehchukene.

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.

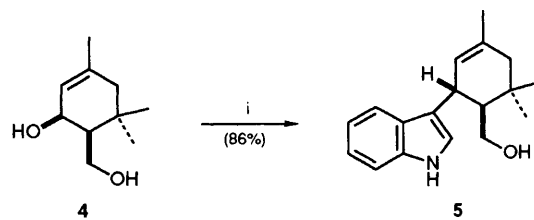
Preliminary experiments demonstrated that no reaction was observed upon exposure of a 0.1 mol dm^{-3} solution of isophorol 2 in freshly prepared 3.0 mol dm^{-3} lithium perchlorate–diethyl ether to 2.0 equiv. of freshly sublimed indole. However, addition of 0.01 equiv. of acetic acid² to the above reaction 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





Scheme 1 Reagents: i, LiClO₄-Et₂O (3 mol dm⁻³), HOAc (0.01 equiv.), indole (2.0 equiv.)



Scheme 2 Reagents: i, LiClO₄-Et₂O (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

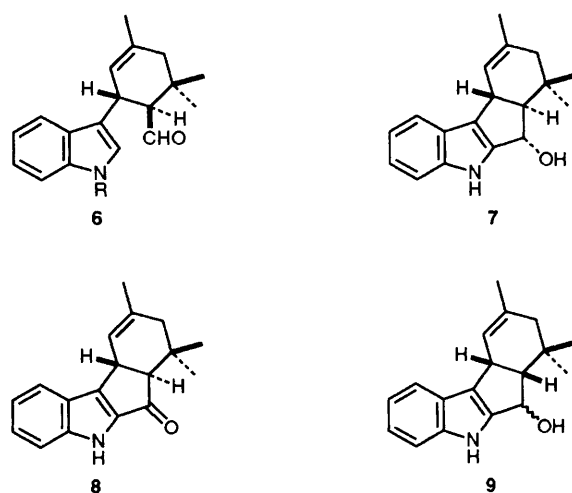
Entry	Substrate	Product	Yield (%) ^b
1			82 ^c
2			90 ^c
3			81
4			97

^a All reactions were conducted at ambient temperature employing a 0.1 mol dm⁻³ solution of substrate in 3.0 mol dm⁻³ LiClO₄-Et₂O 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.

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 Isolated⁵ 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 cyanofornate 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)dipiperidine⁶ afforded after 1 h at ambient temperature an 81% yield of aldehyde **6** (R = H). Benzoylation [BzCl (Bz = benzoyl), Et₃N, 4-dimethylaminopyridine, ClCH₂CH₂Cl, 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 alkoxy magnesium 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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