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Reaction of (dimethylvinylidene)carbene with indole-3-carbaldehyde and its application in the synthesis of β-(dehydroprenyl)indole-based natural products

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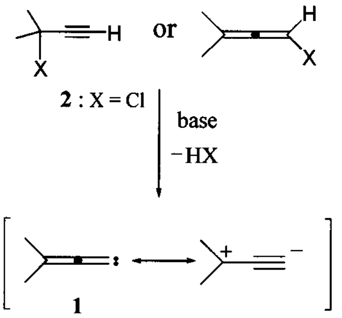
Reaction of (dimethylvinylidene)carbene with indole-3-carbaldehyde gives various dehydroprenyl-based indoles. Efficient synthesis of the indole natural products yuehchukene and murrapanine, using this reaction as a key step, is also described.

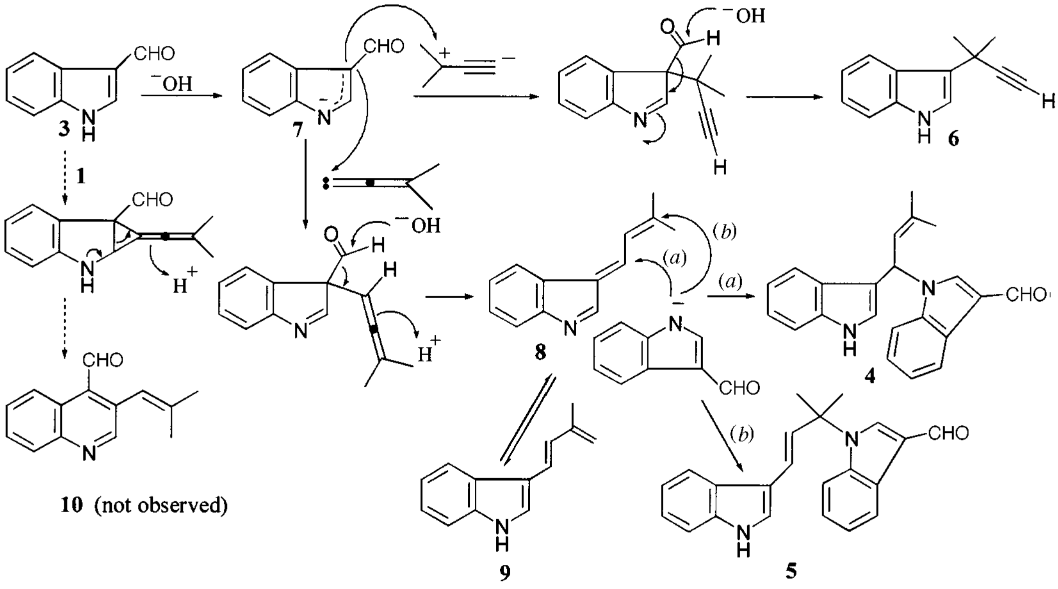
The cyclopropanation of nucleophilic olefins with (dimethylvinylidene)carbene **1**, generated by the elimination of hydrogen halide from propargyl halides or halloallenes (Scheme 1), represents an important carbon–carbon bond-forming process, involving introduction of a dehydroprenyl group into organic substrates,[1–6] and has found use in natural product synthesis.[7,8] Interaction of **1** with indole itself[9] and α- and/or β-methyl indoles has been studied,[10] however, reaction between **1** and indoles containing an electron-withdrawing group at C-2 or C-3 has not been investigated. In connection with our previous studies on the regioselectivity of **1** towards different olefins[11] and synthesis of β-(dehydroprenyl)indoles,[12] we have investigated the reaction of **1** with indole-3-carbaldehyde. We report herein the preliminary results of this work directed to the introduction of a dehydroprenyl unit onto the β-carbon of indole. Application of this reaction in the synthesis of indole natural products containing a β-dehydroprenyl group is also described.



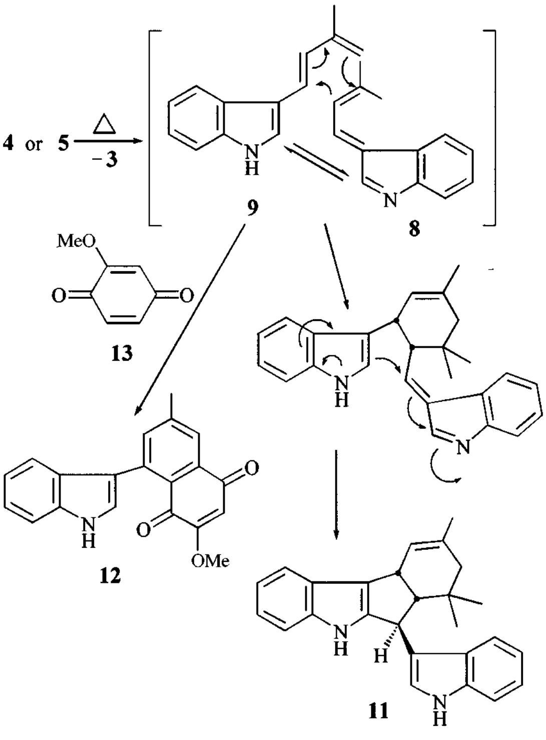
Scheme 1

Treatment of 3-chloro-3-methylbut-1-yne **2** with aq. KOH, a catalytic amount of dibenzo-18-crown-6 and THF in the presence of indole-3-carbaldehyde **3** under reflux gave a mixture which was separated to afford two bis-indoles, 3-[3-methyl-1-(3-formylindol-1-yl)but-2-enyl]indole **4**† (44%) and 3-[(*E*)-3-methyl-3-(3-formylindol-1-yl)but-1-enyl]indole **5**‡ (6%), and 3-(1,1-dimethylprop-2-ynyl)indole **6**[9] (8%). Alkyne **6** was considered to be derived from the electrophilic addition of the carbene **1** at C-3 to the β-carbon of anion **7** and subsequent decarbonylation. Electrophilic addition of the carbene at C-1 to the β-carbon of the indolide anion **7** and subsequent decarbonylation, on the other hand, would lead to the formation of indole **8**, a tautomer of β-(dehydroprenyl)-indole **9**, as the reactive intermediate. Further condensation of anion **7** at the C-2 and C-4 positions of the side-chain of **8** could give β-prenylindoles **4** and **5**, respectively. The mechanism of this reaction was proposed as portrayed in Scheme 2. The formation of **4** and **5** revealed that β-dehydroprenylation of indole had taken place, but that the product was unstable in the form of **8** or its tautomer **9** under the above reaction conditions, and had undergone *in situ* Michael condensation with anion **7**.

Interaction of carbene **1** with α- and/or β-methylindoles, and indole itself, has been shown to give mostly ring expansion of the cyclopropane intermediates, which were assumed to be formed by addition of carbene to the nucleophilic 2,3-double bond of indoles, to give 3-vinylquinolines.[9,10] However, the



Scheme 2



Scheme 3

reaction of **1** with **3** did not give the expected quinoline **10**, probably due to the stronger acidity of indole-3-carbaldehyde **3** in comparison with α- and/or β-methylindoles and indole itself. Thus, interaction of indole **3** with base gave indolide anion **7**, which reacted predominantly *via* nucleophilic attack by C-3 upon carbene **1**, and led to the formation of dehydroprenylindoles and/or the following prenylindoles. This study shows that the presence of an electron-withdrawing group, in this case the formyl group at the β-position of indole, could prevent the formation of quinoline and steer the reaction towards β-alkylation products.

The above reaction provides a new method for the β-prenylation of indole in a simple and efficient manner. Furthermore, elimination of **3** from both **4** and **5** to give β-(dehydroprenyl)indole **9** should be achieved easily as the anion **7** is stable due to delocalisation of the negative charge, and is considered to be a good leaving group. Thus, the above reaction may be useful for the synthesis of β-(dehydroprenyl)indole-base compounds. In order to demonstrate the potential of this carbon–carbon bond-forming reaction we applied the above reaction as a key step in the synthesis of two bioactive indole natural products, yuehchukene **11**[13,14] and murrapanine **12**,[15] which were isolated from *Murraya* species. The structures of these two compounds reveal that they are derived from β-(dehydroprenyl)indole **9**. We found that heating both **4** and **5** in a neutral solution of ethylene glycol at 165–170 °C yielded yuehchukene in 42% yield. Thermal reaction of **4** and **5** with methoxyquinone **13** (3 equiv.) under the above reaction conditions afforded murrapanine in 65% yield. The above one-step reactions are considered to give β-(dehydroprenyl)indole **9** first *via* elimination of **3** (recovered quantitatively), followed by subsequent Diels–Alder reaction (Scheme 3) as described previously.[12] The dehydroprenyl unit of the carbon skeleton of natural products **11** and **12** were constructed completely from carbene **1** in this synthesis. It is worth mentioning here that this is the first synthesis of a dehydroprenylated indole natural products using (dimethylvinylidene)carbene **1** as the isoprenoid unit of the carbon skeleton.

In conclusion this is the first reaction of vinylidenecarbene with indoles having an electron-withdrawing substituent on the 2,3-double bond. The above reaction provides an efficient method for introducing an appropriate 'isoprene' group into the β-position of indole, making use of inexpensive and readily available propargyl chloride **2** and indole-3-carbaldehyde **3** as starting materials. The above result suggests that reaction of vinylidenecarbene with indoles containing different functional groups at C-2 and C-3 should be further investigated. The scope of this chemistry is now being explored in our laboratory.

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Notes and references

† *Selected data* for **4** : ν_{max}(KBr)/cm^{-1} 3256, 1636, 1614, 1386; δ_H(300 MHz, CDCl$_3$) 1.84 (s, 3 H), 1.86 (s, 3 H), 5.68 (d, 1 H, *J* 8.4), 6.56 (d, 1 H, *J* 8.4), 7.04–8.35 (m, 10 H), 8.38 (br s, 1 H, NH), 9.86 (s, 1 H); *m*/*z* 328 (M$^+$).

‡ *Selected data* for **5** : ν_{max}(KBr)/cm^{-1} 3260, 1640, 1612, 1396, 956; δ_H(300 MHz, CDCl$_3$) 1.94 (s, 6 H), 6.48 (d, 1 H, *J* 16.2), 6.70 (d, 1 H, *J* 16.2), 7.12–8.35 (m, 10 H), 8.41 (br s, 1 H, NH), 10.03 (s, 1 H); *m*/*z* 328 (M$^+$).

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