

SYNTHESIS OF TETRAHYDROQUINOLINE DERIVATIVES BY [4+2]CYCLOADDITION REACTION

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Abstract — Tetrahydroquinoline derivatives (4 and 5) were synthesized by Lewis acid catalyzed [4+2]cycloaddition reaction of the olefins (1 and 2) and the imine (3).

A number of biologically interesting compounds bearing a quinoline ring system, such as camptothecin, are widely distributed in nature.

With regard to the synthesis of a quinoline ring, various methods have been reported to date, such as the Skraup synthesis^{1,2}, the Friedlander synthesis³, the Pfitzinger synthesis⁴ and so on⁵. However, little attention has focused on the [4+2]cycloaddition reaction for the synthesis of a quinoline ring, though the reactions of *o*-quinone methide imines with olefins have recently appeared⁶.

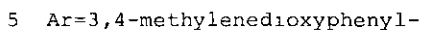
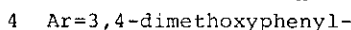
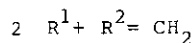
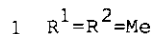
We have investigated the synthesis of a quinoline ring system by employing an intermolecular [4+2]cycloaddition reaction of the styrene derivatives (1 and 2) with the Schiff base (3).

Boron trifluoride etherate catalyzed reaction of *o*-methylisoeugenol (1) with the imine (3), prepared from benzaldehyde and aniline, in toluene for 12 h under reflux afforded 4-(3,4-dimethoxyphenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline (4) as colorless needles, mp 177 - 178 °C, in 29.6 % yield; C₂₄H₂₅NO₂: m/z 359 ($\underline{M}^+$); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹ 3450, 2850, 1605; NMR (CDCl₃) δ 0.57 (3H, d, J=6.5 Hz, CH₃), 2.00 - 2.40 (1H, m, H-3), 3.70 (1H, d, J=11 Hz, H-2 or H-4), 3.80 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 4.10 (1H, d, J=10 Hz, H-2 or H-4), 6.42 - 7.52 (12H, m, 12 x ArH). The stereochemistry of the product was confirmed to be 4 based on its nmr spectrum.

Similarly, the reaction of isosafrol (2) with 3 in *o*-dichlorobenzene for 12 h at 110 - 120 °C gave 5 as colorless needles, mp 178 - 179 °C, in 16.4 % yield;

C₂₃H₂₁NO₂: m/z 343 ($\underline{M}^+$); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹ 3400, 2870, 1600; NMR δ (CDCl₃) 0.58 (3H, d, J=6 Hz, CH₃), 2.00 - 2.30 (1H, m, H-3), 3.71 (1H, d, J=11 Hz, H-2 or H-4), 4.10 (1H, d, J=10 Hz, H-2, or H-4), 5.93 (2H, s, -OCH₂O-), 6.46 - 7.45 (12H, m, 12 x

When these reactions were carried out without the presence of Lewis acid, none of the desired product was isolated. Thus we have succeeded in the preparation of a tetrahydroquinoline ring by [4+2]cycloaddition reaction.



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