HETEROCYCLES, Vol 22, No 2, 1984

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

Tetsuji Kametani, Hajime Takeda, Yukio Suzuki, and Toshio Honda
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41,
Shinagawa-ku, Tokyo 142, Japan

Abstract —— Teterahydroquinoline 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 synthesis[3], the Pfitzinger synthesis[4] and so on[5]. 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 appeared[6].

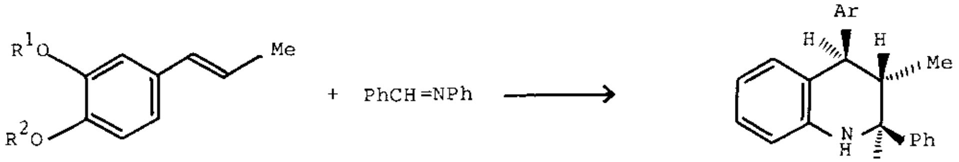
We have investigated the synthesis of a quinoline ring system by employing an intermolecular [4+2]cycloaddition reaction of the styrene derivatives (1 and 2) with the Schiff base (3).

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; $C_{24}H_{25}NO_2$: m/z 359 ($\underline{M}^+$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3450, 2850, 1605; NMR ($CDCl_3$) δ 0.57 (3H, d, J=6.5 Hz, CH_3), 2.00 - 2.40 (1H, m, H-3), 3.70 (1H, d, J=11 Hz, H-2 or H-4), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 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; $C_{23}H_{21}NO_2$: m/z 343 ($\underline{M}^+$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3400, 2870, 1600; NMR δ ($CDCl_3$) 0.58 (3H, d, J=6 Hz, CH_3), 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, $-OCH_2O-$), 6.46 - 7.45 (12H, m, 12 x

ArH).

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.



1 $R^1=R^2=Me$

2 $R^1+R^2=CH_2$

3

4 Ar=3,4-dimethoxyphenyl-

5 Ar=3,4-methylenedioxyphenyl-

ACKNOWLEDGEMENTS We thank Mrs. T. Ogata, Mrs. M. Yuyama, Miss T. Tanaka and Miss M. Moriki of Hoshi University for spectral measurements, microanalyses, and manuscript preparation. This study was supported in part by a Grant-in-Aid for Scientific Research for the Sendai Institute of Heterocyclic Chemistry.

REFERENCES

1. Z.H. Skraup, Monatsh. Chem., 1880, **1**, 316; 1881, **2**, 139.
2. R.H.F. Manske and M. Kulka, Org. Reactions, 1953, **7**, 59.
3. P. Friedlander, Chem. Ber., 1882, **15**, 2572.
4. W. Pfitzinger, J. Prakt. Chem., 1886, **33**, 100.
5. R.C. Elderfield, ed. by R.C. Elderfield, Heterocyclic Compounds, vol. 4, Wiley, New York (1952).
6. D.L. Boger, Tetrahedron, 1983, **39**, 2869 and references cited therein.