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The Synthesis of Tricyclic Naphtho[b] Fused Frameworks via Isoquinolinium Salts

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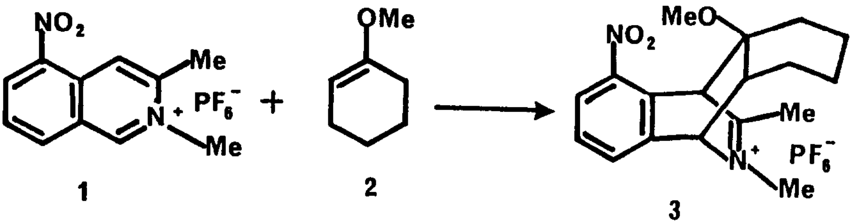
Abstract The cycloaddition of the enol ethers of cyclic ketones with isoquinolinium salts is the key step in a general preparation of interesting tricyclic naphthalene derivatives.

The cycloaddition of isoquinolinium salts with electron-rich alkenes was developed by Bradsher;[1] and it was further extended by Falck,[2] Sammes,[3] and ourselves.[4] Bradsher had reported a limited number of examples where cyclic alkenes participated in the reaction, and only one case where a carbocyclic enol ether adduct was fully characterized; namely salt 1 plus methoxycyclohexene 2 affording adduct 3. We have now broadened the scope of the cyclic alkene version of the Bradsher reaction by adapting some methodologies described by Falck and Sammes for the reaction and its workup. Thus, we report that a wide variety of



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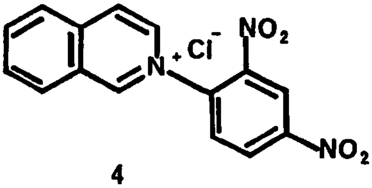

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TABLE

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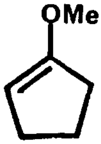
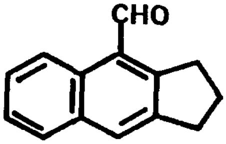
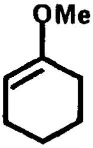
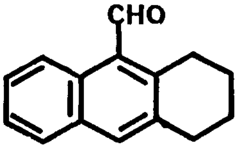
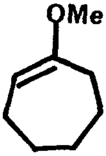
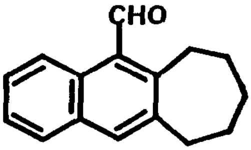
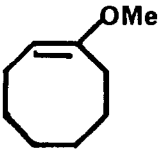
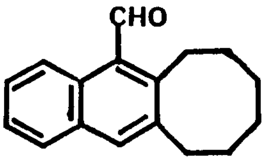
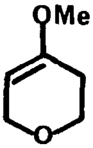
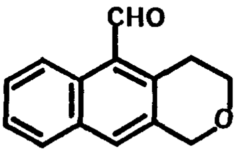
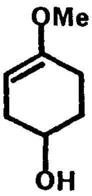
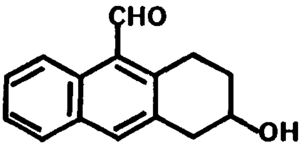
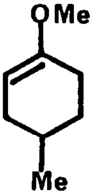
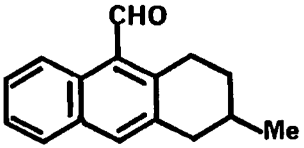
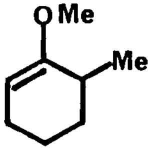
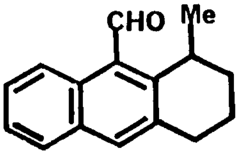
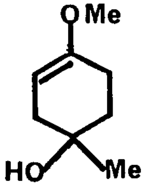
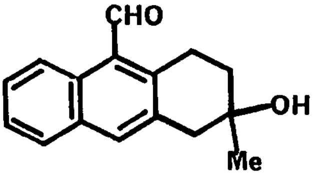
a		5		89
b		5		74
c		5		83
d		5		76
e		6		69
f		7		78

TABLE

Entry	Enol Ether (5)	Ref.	Product (6)	Yield[9]
g		8		82
h		5		16
i		7		62

enol ethers (5) of cyclic ketones can react usefully with isoquinolinium salt 4 as its 2:1 complex with hydroquinone. The addition takes place in methanol at 40° over a period of 3-4 days. Hydrolytic workup of the initial cycloadduct followed by elimination of the elements of methanol and 2,4-dinitroaniline, as described in earlier work,[2,4] affords the naphthaldehyde framework (6). Our results are presented in the Table. Noteworthy is the relative insensitivity of the cycloaddition to ring size of the enol ether. Entry h is the only low-yield example. After the normal reaction period, only the single product 6h and unaffected starting materials were observed. When the reaction was heated to reflux, the isoquinolinium salt 4 was cleaved to produce the mono 2,4-dinitrophenyl ether of hydroquinone. Entry i reveals a tertiary alcohol function which survives the aromatization sequence. The possibility of developing an anthracycline synthesis by the use of cyclic enol ethers with pre-formed A-ring functionality is now being explored.

Bibliography

1.(a) Most recent paper with complete bibliography: Chen, T-K.; Bradsher, C.K., J. Org. Chem., 1979, 44, 4680. (b) Bradsher, C.K., Heterocyclic Compounds, 1981, 38, Part I, Ed. Grethe, G., John Wiley and Sons, NY, 1981, p. 381 ff.

2.(a) Falck, J.R.; Manna S. ; Mioskowski, C., J. Am. Chem. Soc., 1983, 105, 631. (b) Manna, S.; Falck, J.R.; Mioskowski, C., J. Org. Chem., 1982, 47, 5021.

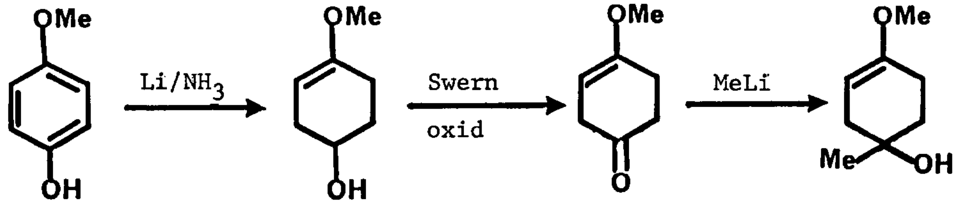
3. Gisby, G.P.; Sammes, P.G.; Watt, R.A., J.C.S. Perkin I, 1982, 249.

4. Franck, R.W.; Gupta, R.B., Chem. Commun., 1984, 761.

5. The enol ethers and their preparation are described: Wohl, R.A.; Synthesis, 1974, 38.

6. Purchased from Aldrich Chemical Co.

7. Reduction of 4-methoxyphenol with lithium and ammonia was carried out according to the procedure of Radlick, P.; Crawford, H.T., J. Org. Chem., 1972, 37, 1669; and the enol ether A was isolated. On Swern oxidation, A gave the ketone B, which on treatment with methyllithium afforded alcohol C.



A B C

8. Prepared from 4-methylcyclohexanone following procedures of ref. 5.

9. Isolated yield; products unambiguously characterized by high-field NMR.

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