Tetrahedron Letters,Vol.27,No.25,pp 2833-2836,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ARYL RADICAL-INITIATED CYCLIZATIONS:

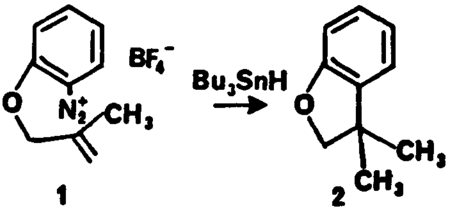
EFFECT OF ARYL SUBSTITUENTS ON RING-SIZE

Kathlyn A. Parker,* Denice M. Spero, and (in part) Karen C. Inman

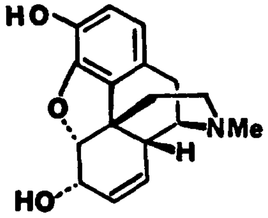
Department of Chemistry, Brown University, Providence, RI 02912

Summary. The presence of a radical stabilizing group on the aryl ring can lead to ring-expanded products.

Although radical cyclization methodology is presently the subject of much attention by the synthetic chemistry community,[1] studies of cyclizations initiated by aryl radicals[2] have not been extensive nor have such cyclizations been exploited for total synthesis. The reported conversion of *o*-methallyloxyphenyl diazonium fluoroborate (1) to 3,3-dimethyl-2,3-dihydrobenzofuran (*2*) by tributyltin hydride prompted us to consider a similar radical cyclization for the construction of the substituted dihydrobenzofuran portion of the carbon skeleton of morphine (*3*).[3] The possibilities of a tandem cyclization[4] which would generate the dihydrofuran ring and the adjacent cyclohexane (B-ring) in a single reaction made this approach especially attractive.



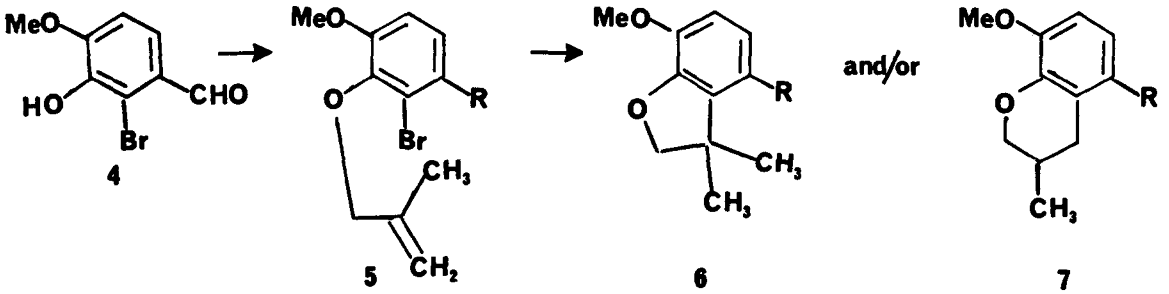
1 2



3

The substrate desired for our projected synthesis would be an ether of a 2-methoxy 5-substituted phenol with a radical initiating group at C-6; the substituent at C-5 would be required for a tandem cyclization. Successful conversion of these materials to dihydrobenzofurans would show that substituents necessary for a facile route to morphine could be tolerated in the cyclization. Ethers derived from the known bromoisovanillin (*4*)[5] were chosen, therefore, for model studies.

Methallyl ether *5a*[6] was prepared by treatment of bromoisovanillin with sodium hydride in DMF followed by addition of methallyl chloride and stirring at 60° for 6 hours.



4

5

a R=CHO

b R=CH_2OH

c R=CN

6

———

b R=CH_2OH

c R=CN

7

a R=CHO

———

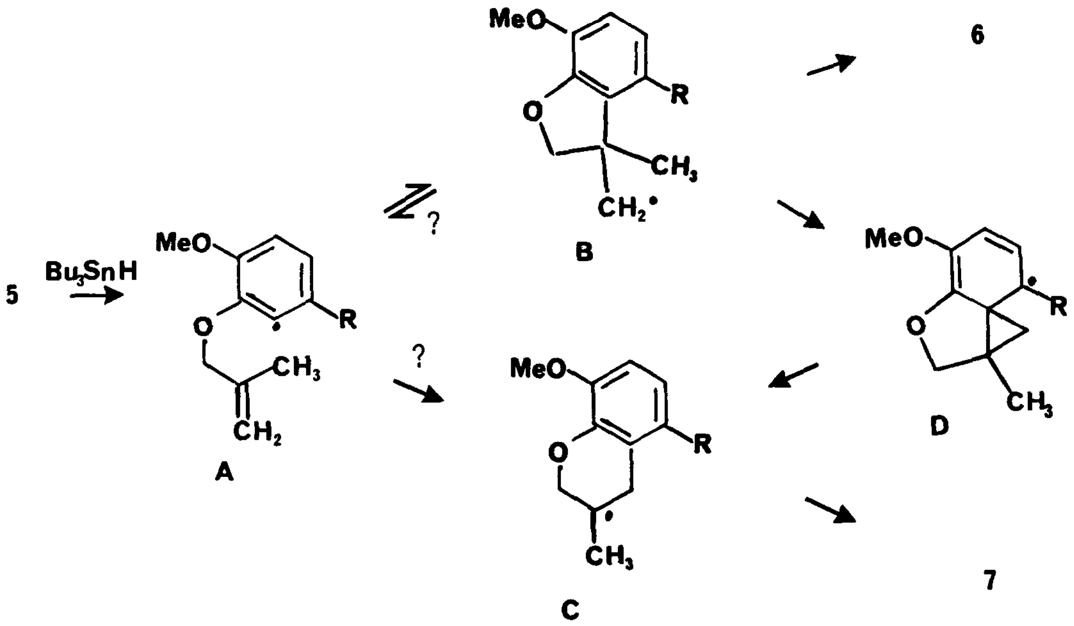
c R=CN

On treatment with tributyltin hydride, bromoarene *5a* was slowly converted to a mixture of starting material and three new materials (ratio 10:1:1). The major component was isolated in 50% yield (corrected for recovery of unreacted starting material) and shown to be the dihydrobenzopyran *7a* (rather than the expected dihydrobenzofuran product *6a*).

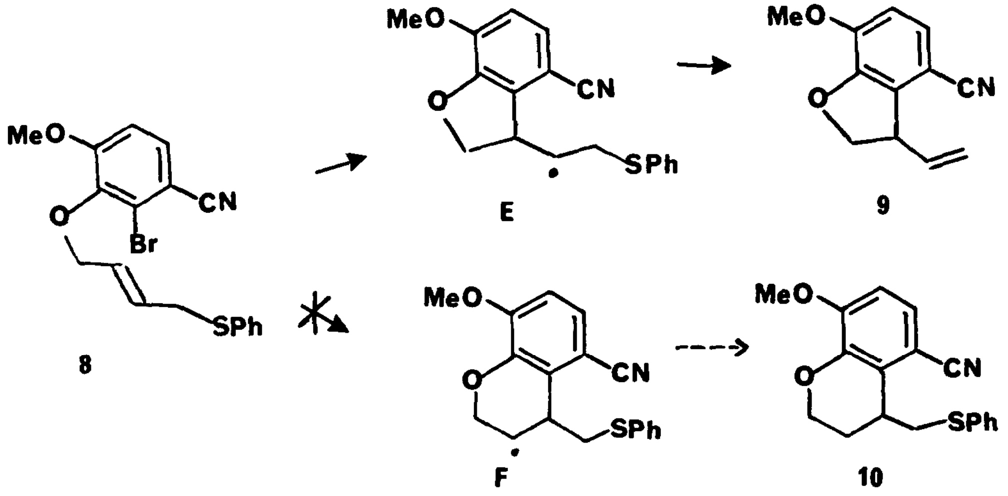
Aldehyde *5a* was converted to alcohol *5b* by sodium borohydride reduction and to nitrile *5c* by the method of Hunt.[7] Cyclization of alcohol *5b* gave a 47% yield of the dihydrobenzofuran product *6b*. Cyclization of nitrile *5c* gave a quantitative recovery of a 60:40 mixture of the dihydrobenzofuran and dihydrobenzopyran products, *6c* and *7c*. From these results, we can conclude that ring-size in the cyclization is determined at least in part by the electronic nature of the *ortho* substituent.

As there is nothing unprecedented in the formation of *6* from *5*, we need only devise a mechanism to account for the formation of *7*. It seems to us that there are two general conditions under which radical C, the immediate precursor of *7* might arise from radical A in a way which is subject to the observed substituent effect.

1. The substituents have altered the relative rates of cyclization of A to B and C.
2. The substituents have increased the tendency of B to rearrange to C (presumably *via* A or *via* D).



We can eliminate mechanism 1 from consideration on the basis of a study with substrate *8*. Treatment of *8* with tributyltin hydride gave a 65% yield of the vinyl dihydrofuran *9*;[8] no dihydropyran product *10* (which would have been expected if radical F had been formed in a kinetic step) was observed. Although we cannot rigorously eliminate the possibility that B rearranges to C *via* A, it seems more likely that B is converted to A through a neophyl rearrangement (*i.e. via* D). This rearrangement is known to be accelerated by substituents which are situated on the ring such that they can stabilize the phenonium radical.[9]



Application of the radical cyclization strategy to the synthesis of dihydrobenzofuran intermediates which might be elaborated to morphine is being pursued.

Acknowledgment This work was supported by the National Science Foundation (Grant No. CHE-8306687). NMR spectra were acquired with a Bruker WM250 spectrometer, purchased with funds from the National Science Foundation and from Montedison, SPA (Milan, Italy).

REFERENCES

1. (a) For a review of "Free Radical Carbon-Carbon Bond Formation in Organic Synthesis", see Hart, D. J., *Science, 1983, 221,* 747. (b) For a review of "Regioselectivity and Stereoselectivity in Radical Reactions", see Beckwith, A. L. J., *Tetrahedron, 1981, 37,* 3073.

2. (a) Beckwith, A. L. J., Gara, W. B., *J. Chem. Soc., Perkin II, 1975,* 593. (b) Beckwith, A. L. J., Gara, W. B., *J. Chem. Soc., Perkin II, 1975,* 795. (c) Beckwith, A. L. J., Meijs, G. F., *J. Chem. Soc., Chem. Commun., 1981,* 136. (d) Beckwith, A. L. J., O'Shea, D. M., Roberts, D. H., *J. Chem. Soc., Chem. Commun., 1983,* 1445. (e) Shankaran, K., Sloan, C. P., Snieckus, V., *Tetrahedron Lett., 1985, 49,* 6001.

3. For other synthetic approaches to the morphine alkaloids, see Schultz, A. G., Lucci, R. D., Napier, J. J., Kinoshita, H., Ravichandran, R., Shannon, P., Yee, Y. K., *J. Org. Chem., 1985, 50,* 217 and references therein. Also Chandler, M., Parsons, P. J., *J. Chem. Soc., 1984,* 322; Stella, L., Raynier, B., Surgur, J. M., *Tetrahedron Lett., 1977,* 2721.

4. (a) Curran, D. P., Rakiewicz, D. M., *J. Am. Chem. Soc., 1985, 107,* 1448. (b) Stork, G., Mook, R., Jr., *J. Am. Chem. Soc., 1983, 105,* 3720. (c) Curran, D. P., Chen, M-H., *Tetrahedron Lett., 1985, 26,* 4991.

5. (a) Hlasta, D. J., Bell, M. R., *Tetrahedron Lett., 1985, 26,* 2151. (b) Pauly, H., *Chem. Ber., 1915, 48,* 2010.

6. All new compounds had ir, nmr and high resolution mass spectra consistent with the structures assigned.

7. Hunt, J. H., *Chemistry and Industry, 1961, 1873.*

8. A similar cyclization with a phenyl ring which bears no electron withdrawing radical stabilizing groups gives a vinyl dihydroindole: Ueno, Y., Chino, K., Okawara, M., *Tetrahedron Lett., 1982, 23,* 2575.

9. Ruchardt, C., Hecht, R., *Tetrahedron Lett., 1962,* 957.

(Received in USA 2 April 1986)