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INTRAMOLECULAR DIELS-ALDER REACTIONS OF THE FURAN DIENE

Kathlyn A. Parker* and Mark R. Adamchuk
Metcalf Laboratories, Brown University, Providence, Rhode Island 02912

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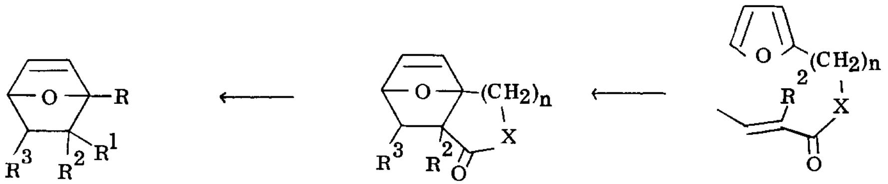
In connection with a program directed toward the synthesis of fused lactones, we needed to prepare substituted oxabicyclo compounds such as 1, the Diels-Alder product of a 2-substituted furan with a suitable dienophile. Bimolecular Diels-Alder reactions of furans[1,2] with olefins activated by only one electron-withdrawing substituent take place slowly with low yields and give mixtures of isomers. As intramolecular cycloadditions[3] exhibit enhanced reactivity and stereoselectivity, we reasoned that an intramolecular Diels-Alder reaction might not suffer the difficulties of addition to the furan diene system and that adducts with the desired substitution pattern might be obtained (3→2→1). In an effort to investigate the scope of the cycloaddition[4], a number of new furan substrates have been prepared and tested for cyclization. The structural requirements for reaction are discussed below.



1 2 3

Substrates in which the furan nucleus and the dienophile are connected by an ester-containing chain showed no evidence of ring closure. Thus 4a, under a variety of conditions (e.g. reflux in Et_2O, EtOH, ØH, DMF, and $CH_2Cl_2/AlCl_3$), and 4b and 5, in refluxing benzene, gave no cyclization product. Likewise, the secondary amides 6a-c gave no cycloadduct in refluxing benzene.

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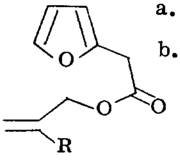

a. $R=CO_2Et$
b. R=H

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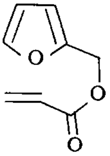

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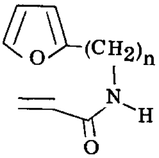
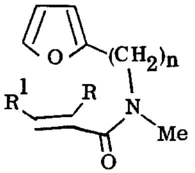


a. n=1
b. n=2
c. n=3

A number of tertiary amides, however, did undergo ring closure. For example, amide 7a[5] cyclized quantitatively[6] during 6 days in refluxing benzene[7]. Amide 7b, substituted in the α position, also gave a quantitative yield of adduct after 5 days in refluxing benzene. Amide 7c bearing a β substituent, underwent only 40% conversion to the cycloadduct after 14 days in refluxing benzene. To test the importance of dienophile activation, substrates 8a-c were investigated. Amide 8a cyclized in quantitative yield (benzene reflux, 6 days) but β-substitution on the dienophile (8b and 8c) precluded cyclization.



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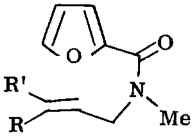
a. n=1, R=H, R'=H
b. n=1, R=Me, R'=H
c. n=1, R=H, R'=Me
d. n=2, R=H, R'=H
e. n=2, R=H, R'=Me
f. n=3, R=H, R'=H
g. n=3, R=H, R'=Me



8

a. R=H, R'=H
b. R=Me, R'=H
c. R=H, R'=Me

Closure to six-membered lactams worked well but formation of seven-membered rings was inhibited. Thus, 7d afforded a quantitative yield of product after 4 days at benzene reflux but 7f gave only 45% conversion after 6 days. The additional energy barrier (or product instability) associated with a β substituent limited the conversion of 7e to 12% while 7g underwent no detectable reaction.

In order to examine the influence of the size of the N-alkyl group, N-benzyl amide 9 was prepared. Amide 9 underwent 75% conversion to cyclized product (compared to 45% for 7f). This is in agreement with the entropic effect of the N-substituent noted previously for substituted pentadienylacrylamides.[8]

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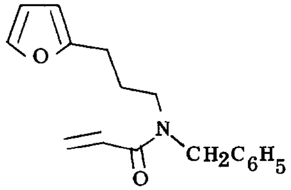

Finally, to ascertain the potential diversity of the cyclization, diester 10, consisting of an all-carbon connecting chain was prepared. Reaction was found to occur with 40% conversion after 5 days in refluxing benzene.

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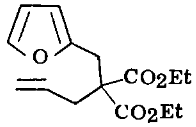

We may draw several conclusions concerning the requirements for reactivity of furan dienes in the intramolecular Diels-Alder reaction. As cycloaddition can occur only when the substrate adopts a conformation in which the furan and the dienophile are geometrically disposed for π overlap, reactivity in the cycloaddition is heavily dependent on factors which favor this conformation. Thus, substrates in which the sidechain contains an ester moiety are unreactive, presumably because the molecule prefers the unreactive conformation in which diene and dienophile are transoid about the ester linkage.[9] A similar conclusion may be drawn with respect to the secondary amides.[10] However, tertiary amides, the substituted malonate 10 and tertiary amines[4b,d] are all capable of achieving the required conformation of diene and dienophile and hence undergo cycloaddition. Within these structural limitations, significant chain variation is possible. Five, six, and seven-membered rings can be formed and in the five-membered cases, the amide carbonyl can be adjacent to either the diene or the dienophile. In addition, α substitution in the dienophile does not appear to retard reaction. Substrates with a trans β-substituent afford lower yields.

Besides influencing reactivity, the constraints imposed by the connecting bridge also serve to limit the number of stereoisomers. Only one of two regioisomers is possible and, in the cases studied so far, one stereoisomer is preferred. Based on models[4e] and spectral analogy, this preference, at least in the five-membered ring amides, is for the exo mode of cyclization (trans ring junction). The coupling constant between protons H_a and H_b in adduct 11 (from 7c) is 5 Hz., suggesting a dihedral angle of 40° (according to models, the corresponding angle for the alternative structure would be about 90° resulting in no splitting). This is in agreement with spectral data presented by Bilovic[4c] for a related set of compounds.

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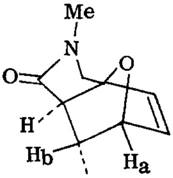

In summary, the intramolecular Diels-Alder reaction of furans has been extended to include a number of new substrates and some of the factors influencing reactivity have been identified. Further work on elaboration of these intermediates is in progress.

References and Notes

1. a) F. Kienzle, Helv. Chim. Acta, 58, 1180 (1975).
   b) M. P. Kunstman, D. S. Tarbell, and R. L. Autrey, J. Am. Chem. Soc., 84, 4115 (1962).

2. Recently, Dauben (W. G. Dauben and H. O. Krabbenhaft, J. Am. Chem. Soc., 98, 1993 (1977)) reported that the use of very high pressures affords moderate yields with olefins activated by one electron-withdrawing group.

3. For recent reviews of the intramolecular Diels-Alder reaction, see:
   a) W. Oppolzer, Angew. Chem., Int. Ed Engl., 16, 10 (1977).
   b) R. G. Carlson, Ann. Rep. in Med. Chem., 270 (1974).

4. Although a limited number of examples of the intramolecular Diels-Alder reaction of the furan nucleus have been reported, no systematic study has appeared. See:
   a) H. H. Wasserman and A. R. Doumaux, J. Am. Chem. Soc., 84, 4611 (1962).
   b) D. Bilovic, Z. Stojanac, and V. Hahn, Tetrahedron Lett., 2071 (1964).
   c) D. Bilovic, Croatica Chemica Acta, 40, 15 (1968).
   d) Z. Klepo and K. Jacopcic, Croatica Chemica Acta, 47, 45 (1975).
   e) H. W. Gschwend, M. J. Hillman, and B. Kisis, J. Org. Chem., 41, 104 (1976).

5. Substrates 4a, 7a, 7b, 7d, 7f, 8b, 9, and 10 and the cycloadducts of 7a, 7b, 8a, and 9 were characterized by spectra and combustion analysis. All other compounds gave satisfactory ir and nmr spectra. Cycloadducts in reactions that did not go to completion were not usually isolated; the extent of conversion was estimated from the nmr spectrum of the product mixture.

6. "Quantitative" refers to the yield of crude material after removal of benzene. In general, reactions were followed by tlc or nmr and stopped when no further reaction was apparent. In all cases, only cycloadduct and starting material were seen by tlc and nmr.

7. These conditions were chosen as standard in order to compare relative reactivities. No effort was made to optimize yields.

8. H. W. Gschwend, A. O. Lee, and H-P. Meier, J. Org. Chem., 38, 2169 (1973).

9. M. Simonetta and S. Carra, "General and Theoretical Aspects of the COOH and COOR groups" in The Chemistry of Carboxylic Acids and Esters, S. Patai, editor, New York, Interscience, 1969, p. 13.

10. M. B. Robin, R. A. Bovey, and H. Basch, "Molecular and Electronic Structure of the Amide Group" in The Chemistry of Amides, J. Zabicky, editor, New York, Interscience, 1970. p. 19.