THERMAL CYCLOADDITIONS OF DIMETHYL ACETYLENEDICARBOXYLATE WITH CYCLIC ENOLETHERS. AN ENTRY INTO MEDIUM SIZE OXOCYCLIC SYSTEMS

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Summary. Thermal cycloaddition of dimethyl acetylenedicarboxylate with a series of cyclic enolethers gave the corresponding bicyclic compounds which were expanded to medium size oxocyclic systems by further thermolysis or Lewis acid catalysis.

During a program directed towards the total synthesis of a number of marine natural products containing oxocyclic systems, we had the opportunity to explore a number of new approaches to these systems. In this communication we report a new entry into 7-and 8-membered ring ethers from 5- and 6-membered endocyclic enolethers respectively via 2+2 cycloaddition¹ with dimethyl acetylenedicarboxylate, followed by ring expansion. **Eq. 1** (**Table 1**) exemplifies the sequence for the case of the 8-membered ring oxocyclic systems and **Table 1** lists a number of examples. Thus, when dimethyl acetylenedicarboxylate (II) and 3,4-dihydro-2H-pyran (I, R=H, sevenfold excess) were heated in toluene² (sealed tube, 180°C external temperature, 16h) products III (R=H) and IV³ (R=H) were isolated in 36 and 24% yield respectively, after flash column chromatography⁴. Although the bicyclic system III (R=H) could be converted to the monocycle IV (R=H) by further heating, it was found that EtAlCl₂ catalyzed this ring expansion quite efficiently at 25°C (81% yield). On the other hand, the 2-substituted enolethers I (**Table 1**), entries 4-6) upon heating in refluxing xylene led directly to the ring-expanded products **IV**, presumably via the intermediacy of **III**.

The 5-membered ring enolethers V (R=H, Me, **Table 2**, **Eq. 2**) also underwent the cycloaddition reaction, leading to the bicyclic systems VI (R=H, 39%; R=Me, 41%) in addition to dienes VIII (R=H, 22%; R=Me, 27%). These observations are in accord with results previously reported by Gollnick and Fries⁵ for 5-methyl-2,3-dihydrofuran. The use of more forcing conditions (PhMe, 110°C, sealed tube) were found to be necessary for the reaction of 2,3-dihydrofuran, whereas the addition of ⁱPr₂NEt in catalytic amounts enhanced the yields of these reactions. Furthermore, in the case of 5-methyl-2,3-dihydrofuran it was found that polar solvents such as DMF and DMSO increased both the rate of the reaction and the yield of the cycloaddition product (VI) in expense of the open adduct (VIII) (see **Table 2**). These observations are in agreement with the previously postulated polar mechanism for these reactions⁵.

Subsequent thermolysis of bicyclic compound VI (R=Me) at 200°C led to the oxepane derivative VII³ (R=Me, 85%) as indicated in **Table 2**. Noteworthy is the resistance of the parent compound VI (R=H) to thermal opening, even at 700°C (flash pyrolysis). The more facile disrotatory ring opening of the pyranyl bicyclic systems is in line with earlier results involving carbocyclic analogs⁶. Also, it appears that alkyl groups at the 2-position accelerate ring expansion in both the 8-and 7-membered ring series⁷.

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Table 1. Synthesis of 8-Membered Oxocyclic Systems







References and Notes

- 1. For a photochemically-induced, low yield cycloaddition of dihydropyran and dimethyl acetylenedicarboxylate see: R.P. Gandhi, V.K. Chadha Indian J. Chem. 1968, 6, 402.
- For an unsuccessful attempt to react dimethyl acetylenedicarboxylate with 3,4-dihydro-2Hpyran see: S.S. Hall, A.J. Duggan J. Org. Chem. 1974, 39, 3432.
- 3. N.m.r. (250MHz, CDCl3, TMS). IV (R=H): δ 7.61 (s, 1H, O-C<u>H</u>=), 6.69 (dd, J=9.0, 9.0Hz, 1H, C<u>H</u>=C-COOMe), 4.60 (bt, J=12.0Hz, 1H, C<u>H</u>2-O), 4.05 (dd, J=12.0, 5.5Hz, 1H, C<u>H</u>2-O), 3.75, 3.67 (2xs, 2x3H, 2x COOC<u>H</u>3), 2.50 (m, 2H, C<u>H</u>2-CH=), 2.06 (m, 1H, C<u>H</u>2), 1.29 (m, 1H, C<u>H</u>2); VII (R=Me): δ 6.99 (t, J=5.5Hz, 1H, C<u>H</u>=), 4.34 (dd, J=5.0, 5.0Hz, 2H, C<u>H</u>2-O), 3.77, 3.73 (2xs, 2x3H, 2xCOOC<u>H</u>3), 2.62 (m, 2H, C<u>H</u>2-CH=), 2.24 (s, 3H, C<u>H</u>3).
- 4. For similar Lewis acid-catalyzed cycloadditions of silylenol ethers see: R.D. Clark, K.G. Untch *J. Org. Chem.* **1979**, *44*, 248.
- 5. K. Gollnick, S. Fries Angew. Chem. Int. Ed. 1980, 19, 832.
- O.L. Chapman, D.J. Pasto, G.W. Borden, A.A. Griswold J. Am. Chem. Soc. 1962, 84, 1220; J.S. McConaghy, Jr., J.J. Bloomfield Tetrahedron Lett. 1969, 3719.
- 7 New compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

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