CHEMISTRY LETTERS, pp. 223-226, 1987.

Two-Step Synthesis of Furans by Mn(III)-Promoted Annulation of Enol Ethers†

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Enol ethers, β-dicarbonyl compounds and the Mn(III) reagent $Mn_3O(OAc)_7$ react under mild conditions to form 1-alkoxy-1.2-dihydrofurans in good (70-98%) yields. The latter are readily converted to furans by acid-catalyzed elimination of ROH.

Furan derivatives have been the subject of increasing attention because of their utility in synthesis,$^{1)}$ their occurrence in many natural products, and their ever greater synthetic accessibility.$^{2)}$ This note describes a simple two-step route to types of substituted or polycyclic furans which are not easily available by other methods.

In connection with studies on the carboannulation of enol ethers to form fused ring 2-cyclopentenone derivatives we had occasion to investigate the Mn(III)-promoted coupling of β-dicarbonyl compounds$^{3)}$ with enol ethers. This proved to be an efficient route to 1-alkoxy-1,2-dihydrofurans, in contrast to the corresponding reaction with simple olefins which proceeds in low or at best modest yield.$^{3)}$ Thus for example, reaction of 1-methoxycyclohexene (**1**) with ethyl acetoacetate (1.7 equiv.) and $Mn_3O(OAc)_7$ (2.2 equiv.) dissolved in acetic acid at 23 °C under N_2 for 10 min afforded after extractive isolation and filtration through silica gel (1:3 ethyl acetate-hexane) 86% yield of adduct **2**. This adduct was smoothly transformed into the furan **3** (92% yield) by heating at 50 °C with THF-H_2O-HOAc(4:2:1) for 2 h. Alternatively the conversion of **2** to **3** could be effected by heating with 5% aqueous sulfuric acid containing just sufficient methanol to solubilize **2** at 55 °C for 3h. 1-Methoxycyclopentene (**4**) and 1-methoxycycloheptene (**7**) were converted to the dihydrofurans **5** and **8**, respectively, and thence to furans **6** and **9** in the indicated yields using the conditions described for 1-methoxycyclohexene (**1**). Unfortunately t-butyldimethylsilyl enol ethers corresponding to **1**, **4**, or **7** are much less reactive than methyl enol ethers. In acetic acid as solvent silyl ether cleavage to ketone occurs at a rate which is much faster than $Mn_3O(OAc)_7$-promoted addition of ethyl acetoacetate. Nor can conversion of silyl enol ethers to 1-silyloxy-1,2-dihydrofuran adducts be effected in acetonitrile as solvent. Simple 1,2-disubstituted olefins such as cyclohexene are unreactive to ethyl acetoacetate and $Mn_3O(OAc)_7$ either in acetic acid or acetonitrile.

Acetylacetone (**10**), dimethyl or diethyl acetonedicarboxylate (**11**) and 5,5-

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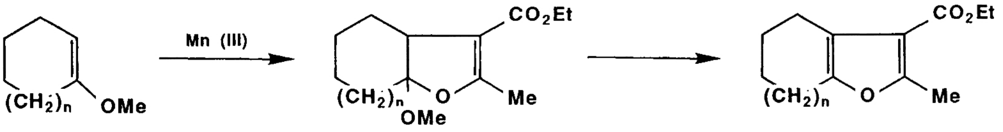
† Dedicated to Professor Teruaki Mukaiyama with best wishes on the occasion of his 60th birthday.

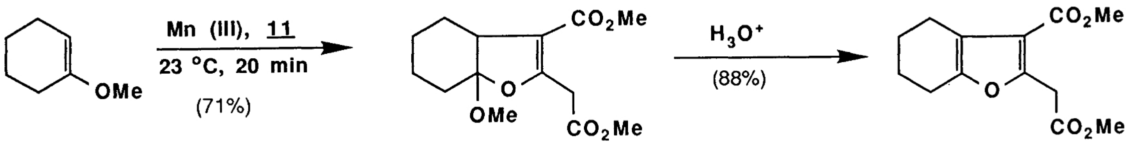
dimethylcyclohexane-1,3-dione (**12**) were all found to be satisfactory 1,3-dicarbonyl components for Mn(III) promoted cycloaddition to enol ethers **1**, **4**, or **7**. Typical results are shown below for the synthesis of furans **13**, **14**, and **15**.



1, n = 1	2, n = 1 (86%)	3, n = 1 (92%)
4, n = 0	5, n = 0 (79%)	6, n = 0 (95%)
7, n = 2	8, n = 2 (79%)	9, n = 2 (97%)

Simple acyclic enol ethers such as ethoxyethylene or 2-methoxypropene also react smoothly with β-dicarbonyl compounds and Mn(III) to form adducts. These reactions are exemplified by the synthesis of the substituted furans **16**, **17**, and **18**.

The route to furans described above is flexible and well suited to convergent synthesis of polycyclic furan compounds. The mildness of the reaction conditions and the predictability of product structure are also important features.



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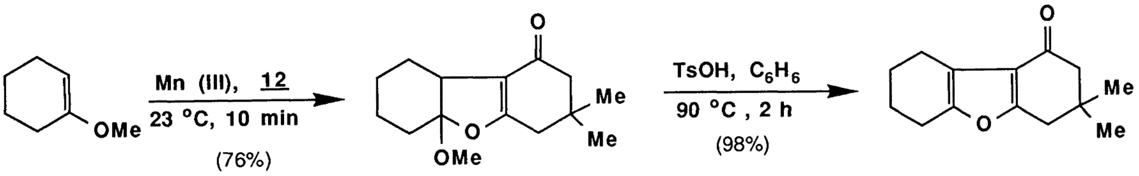
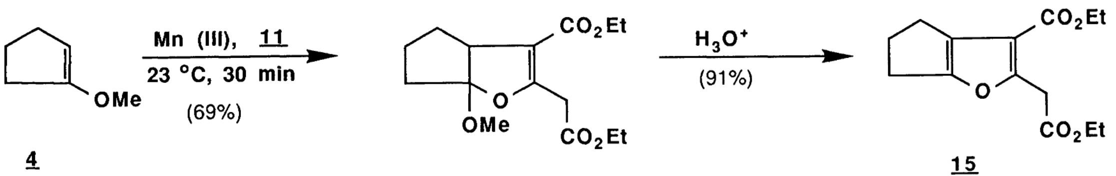
13



1

14a

14



4

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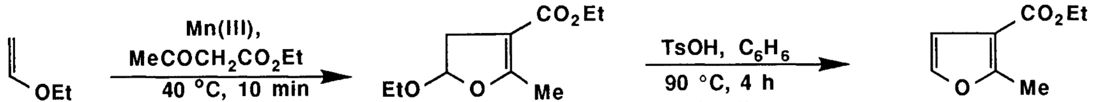
The question of mechanism of these conversions of enol ethers to dihydrofurans is also interesting. The fact that enol ethers but not silyl enol ethers react seems to argue against a mechanism in which a carbon free radical, RCOC HCOR',3) is the species which attacks the enol ether since such a radical is not expected to be so discriminating. A more likely possibility is that an intermediate formed by coordination of the enolic carbonyl reactant with the Mn(III) reagent (through an oxygen-Mn bond) possesses sufficient radicaloid reactivity to attack the enol ether component. Procedures for the preparation of the Mn(III) reagent4) and for illustrative dihydrofuran and furan forming experiments follow.5,6)



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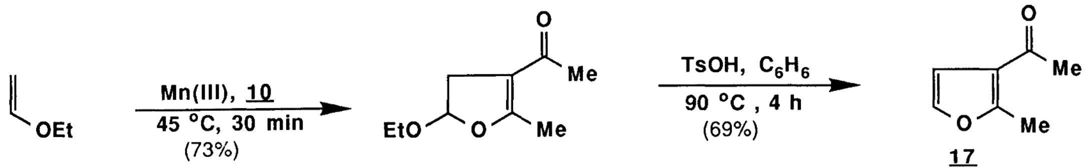

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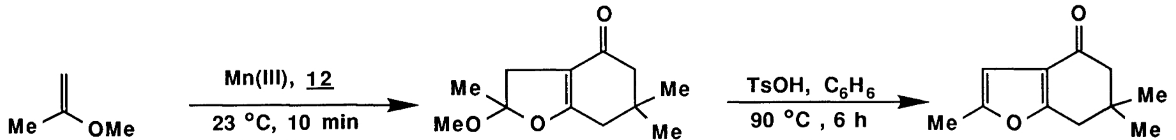

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Acetic anhydride (80 g) was stirred mechanically and heated in a bath to 100 °C, and a 50% aqueous solution of manganous nitrate (14 g) was added dropwise over period of 1 h. During the addition nitrogen dioxide was evolved. Stirring and heating are continued until there was no further gas evolution (ca. 1 h). The viscous solution was cooled and allowed to stand overnight at 23 °C. Manganese(III) acetate which precipitated was removed by filtration, washed with (1) acetic anhydride and (2) anhydrous ether and dried in vacuo; yield of dark brown powdery $Mn_3(OAc)_7$ HOAc, 6.8 g (60%).

Manganese(III) acetate (1.2 g, 4.5 mmol) was dissolved in glacial acetic acid (5 ml) at 40 °C under an argon atmosphere. The resulting solution was cooled to room temperature and was treated with 308 mg (2.2 mmol) of 5,5-dimethyl-1,3-cyclohexanedione and 295 mg (2.6 mmol) of enol ether **1**. The reaction mixture was stirred at room temperature for 20 min at which time the dark brown color of manganese(III) disappeared. The solvent was removed under reduced pressure and the residue was diluted with 2 ml of saturated sodium bicarbonate solution and extracted with ethyl acetate (2 X 5 ml). The combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography over silica gel with 25% ethyl acetate in hexanes as eluent to afford 418 mg (76%) of a 2:1 diastereomeric mixture of dihydrofurans **14a** as a colorless oil. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 3.4 (s, 3H, minor), 3.3 (s, 3H, major), 3.2 (m, 1H, minor), 3.0(m, 1H, major), 2.5 (s, 2H, minor), 2.4 (s, 2H, major), 2.2(s, 2H, minor), 2.15 (s, 2H, major), 2.0 (m., 2H), 1.8-1.3 (m, 6H), 1.12 (s, 3H, major), 1.1 (s, 3H, major), 1.1 (s, 3H, minor), 1.0 (s, 3H, minor). IR (thin film): 2950, 1675, 1600, 1400, 1240 cm^{-1}; MS (70 eV): 250 (M$^+$), 235, 222, 218.

To a stirred solution of 71 mg (0.28 mmol) of dihydrofuran **14a** in dry benzene (5 ml) was added 50 mg of p-toluenesulfonic acid. The mixture was stirred at reflux for 2 h and then cooled to room temperature and added to saturated sodium bicarbonate solution (1.5 ml). The organic layer was separated, the aqueous layer was extracted with ether and the combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. Evaporation of solvent gave an oily residue which was purified by silica gel chromatography with 25% ethyl acetate in hexanes to yield 60 mg (98%) of furan **14** as a colorless oil. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 2.7 (s, 2H), 2.6 (m, 4H), 2.3 (s, 2H), 1.9-1.6 (m, 4H), 1.2 (s, 6H). IR (thin film): 2960, 1680, 1550, 1400, 1360 cm^{-1}; MS (70 eV): 218 (M$^+$), 190, 162, 134.

References

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5) For other recent applications of the Mn(III) reagent in synthesis see: E. I. Heiba, R. M. Dessau, and P. G. Rodewald, J. Am. Chem. Soc., **96**, 7977 (1974); E. J. Corey and M. Kang, ibid., **106**, 5384 (1984); E. J. Corey and A. W. Gross, Tetrahedron Lett., **26**, 4291 (1985); B. B. Snider, R. Mohan, and S. A. Kates, J. Org. Chem., **50**, 3659 (1985).

6) This research was assisted financially by a grant from the National Science Foundation.

(Received October 6, 1986)