Pergamon

Tetrahedron, Vol. 52, No. 38, pp. 12495-12498, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00728-4

Synthesis of Fused Acetals by Ceric Ammonium Nitrate Mediated Cycloaddition of 1,3-Dicarbonyl Compounds to Cyclic Enol Ethers

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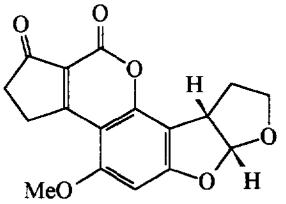
Abstract : Treatment of β-diketones and β-ketoesters with ceric ammonium nitrate and sodium hydrogen carbonate in acetonitrile leads to the formation of intermediates which add efficiently to cyclic enol ethers to furnish fused acetals in good yields.

The synthesis of fused acetals have attracted a considerable attention to organic chemists in recent years, because the furofuran moiety is an important subunit in wide range of biologically active natural products.[1] The aflatoxins, such as aflatoxin B2 (**1**), having a furobenzofuran subunit, attracted early interest[2] and their potential mitotoxicity and significant health hazards have led to a continued synthetic activity.[3] The observed biological activity of relatively simple fused acetals emphasizes the importance of the synthesis of both natural products and their fused acetal sub-fragments. Recently, a general method based on rhodium carbenoid dipolar cycloaddition has been developed[4] for the synthesis of such fused acetals and its potential application to aflatoxins synthesis was noted.[5] Very recently, manganic acetate mediated additions of 1,3-dicarbonyl compounds to endocyclic enol ethers for the synthesis of fused acetal derivatives has been reported.[6]

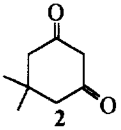
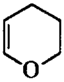
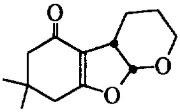
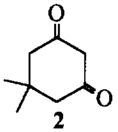
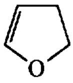
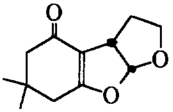
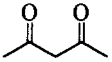
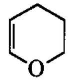
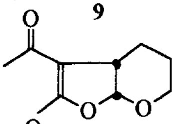
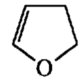
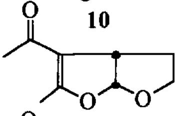
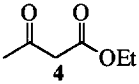
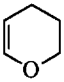
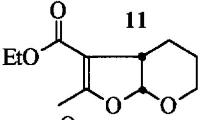
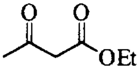
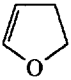
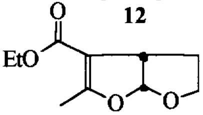
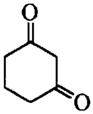
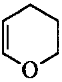
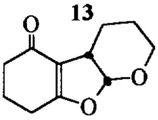
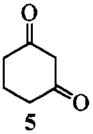
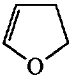
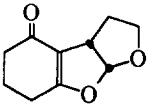


1

Recently, we have demonstrated[7] a general method of preparation of substituted tetrahydrofurans by ceric ammonium nitrate (CAN) mediated cycloaddition of 1,3-dicarbonyl compounds to cinnamic esters. Now we report that fused acetal derivatives can efficiently be synthesized by CAN promoted cycloaddition of β-diketones or β-ketoesters to cyclic enol ethers in good yield. Thus, treatment of the dicarbonyl compound with cyclic enol ether in the presence of 1.2 equivalent of CAN and excess of $NaHCO_3$ in CH_3CN at 0^0C for 2h afforded fused acetal in good yield.

Readily available cyclic enol ethers, dihydropyran **6** and dihydrofuran **7** were chosen as suitable substrates and they were allowed to react separately with four different 1,3-dicarbonyl compounds, dimedone **2**, acetylacetone **3**, ethyl acetoacetate **4** and 1,3-cyclohexane dione **5** via ceric ammonium nitrate mediated radical addition to afford the corresponding fused acetals. The results are summarized in table 1. The spectral data (IR, ^{1}HNMR) of **8**, **10**, **11**, **12**, **13** and **15** are consistent with the reported values.[4,6] Dihydrofuran **7** reacted with dimedone **2** in CH_3CN at 0°C for 2h in the presence of CAN and excess of $NaHCO_3$ to furnish after and chromatography the fused acetal **9** in 67% yield as a crystalline solid, mp 103-104°C. In ^{1}HNMR spectrum, the acetal methine proton appeared as a doublet (J = 7 Hz) at δ 6.23 which is consistent with the values found in

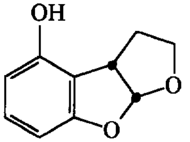
Table 1: CAN mediated cycloaddition of 1,3-dicarbonyl compounds to cyclic enol ethers [a]

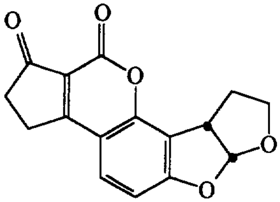
Entry	1,3-dicarbonyl compounds	Cyclic enol ethers	Products	Yield %
1	 **2**	 **6**	 **8**	68
2	 **2**	 **7**	 **9**	67
3	 **3**	 **6**	 **10**	70
4	 **3**	 **7**	 **11**	68
5	 **4**	 **6**	 **12**	65
6	 **4**	 **7**	 **13**	60
7	 **5**	 **6**	 **14**	75
8	 **5**	 **7**	 **15**	75

[a] yields refer to chromatographically pure isolated products

related fused acetals. Similarly, the dione **5** reacted with **6** in the presence of CAN under identical reaction conditions to afford the acetal **14** as a viscous oil in 75% yield. In ^{1}HNMR spectrum, the acetal methine proton appeared as a doublet (J = 8 Hz) at δ 5.90. In all of the cases only *cis* fused acetals were obtained as observed earlier.[4-7] Although similar type of cycloadditions mediated by manganic acetate has been reported,[6] the present method is much superior to that. In all of the cases yields of the acetals are higher in our method and it does not need any acid such as acetic acid which can affect the acid labile functional groups present in the molecule. Moreover, $NaHCO_3$ has been used to minimize the acidity of the reaction mixture. The reactions were performed at low temperature, so no side products or decompositions of the products were observed.

The conversion of the acetal **15** to the phenol **16** has already been done by Kraus and co-workers[3d] by using $CuCl_2$ in 22% yield and they have also synthesized the demethoxyaflatoxin B2 **17** from **16**.We prepared the phenol **16** from **15** in two steps with higher yield. Thus, treatment of **15** with Br_2 in Et_2O at 0°C afforded a crude mass which without further purification was stirred with 10% methanolic KOH at room temperature to give the phenol **16** in 46% yield. The spectral data are identical with the reported values.


16


17

In conclusion, we have developed an efficient and mild method for the preparation of fused acetals by ceric ammonium nitrate mediated cycloaddition of 1,3-dicarbonyl compounds to cyclic enol ethers in good yield. These acetals would produce valuable intermediates for aflatoxins.

Acknowledgement : We thank CSIR, New Delhi for financial support [Grant No. 01(1313)/94/EMR-II]. P.K.M. is a JRF under the above project.

Experimental

Melting points were determined in capillary tubes and are uncorrected. IR spectra were determined with a Perkin-Elmer 298 spectrometer. ^{1}H NMR spectra were recorded in a Varian EM 360L instrument in $CDCl_3$ with TMS as internal reference. Chemical shifts were expressed in ppm, coupling constants in Hz. Solvents and reagents were purified by standard procedures as necessary. Column chromatography was performed on silica gel (60-120 mesh). Petroleum ether of boiling range from 60°C to 80°C was used for column chromatography.

General Procedure : A solution of the 1,3-dicarbonyl compound (1.0 mmol) and the cyclic enol ether (1.2 mmol) in CH_3CN (10 ml) was added dropwise to a stirred mixture of CAN (2.1 mmol) and $NaHCO_3$ (4.0 mmol) in CH_3CN (10 ml) at 0°C . The reaction mixture was stirred at 0°C for 2h, diluted with CH_3CN (50 ml) and filtered. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography over silica gel (30% ethyl acetate in petroleum ether) to afford the pure fused acetal.

***cis*-(3a,8a)-6,6-Dimethyl-2,3,3a,4,5,6,7,8a-octahydrofuro[2,3-b]benzofuran-4-one 9.** Crystalline solid, m.p. 103-104°C. IR (KBr) ν_{max} 2960, 2880, 1655, 1635, 1400, 1250, 1220, 1080 cm^{-1}. ^{1}H NMR δ 1.13 (6H, s), 1.93-2.10 (2H, m), 2.20 (2H, s), 2.30 (2H, d, J=2 Hz), 3.46-4.23 (3H, m), 6.23 (1H, d, J=7 Hz). Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found : C, 69.19; H, 7.65.

***cis*-(4a,9a)-3,4,4a,5,6,7,8,9a-Octahydro-2H-pyrano-(2,3-b)-benzofuran-5-one 14.** Viscous oil. IR (neat) ν_{max} 2950, 2880, 1630, 1400, 1230, 1180, 1120, 1060 cm^{-1}. ^{1}H NMR δ 1.36-2.83 (10H, m), 2.86-3.30 (1H, m), 3.76 (2H, t, J=7 Hz), 5.90 (1H, d, J=8 Hz). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found : C, 67.69; H, 7.36.

***cis*-(3a,8a)-4-Hydroxy-2,3,3a,8a-tetrahydro-furanobenzofuran 16.** A solution Br (293 mg, 1.83 mmol) in Et_2O (30 ml) was added dropwise to a stirred solution of **15** (330 mg, 1.83 mmol) in Et_2O (20 ml) at 0°C. The reaction mixture was stirred for an additional 2.5h at 0°C and then washed with saturated aqueous $Na_2S_2O_3$ (2x15 ml), brine (2x15 ml) and finally dried over Na_2SO_4. Solvent was removed to afford a crude mass (350 mg) which without further purification was stirred at room temperature with 10% methanolic KOH (20 ml) for overnight. Methanol was removed under reduced pressure and the residue was extracted with Et_2O (2x15 ml) to remove the neutral part. The alkaline part was acidified with concentrated HCl and was extracted with Et_2O (4x15 ml). The ether layer was washed with brine (2x15 ml) and dried (Na_2SO_4). Removal of solvent afforded **16** (150 mg, 46%).

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(*Received in UK* 6 *June* 1996; *accepted* 8 *August* 1996)