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Regio and Stereoselective Formation of Dihydrofurans by Ceric Ammonium Nitrate Mediated Oxidative [3+2] Cycloaddition of 1,3-Diketones to Cinnamic Esters

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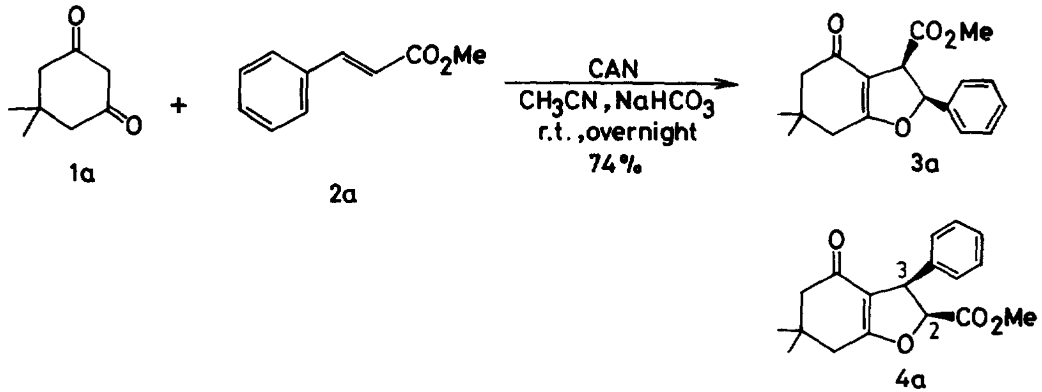
Abstract : Regio and stereoselective syntheses of dihydrofurans were accomplished by ceric ammonium nitrate mediated oxidative [3+2] cycloaddition of 1,3-diketones to cinnamic esters in high yield.

The introduction of radical methodology in synthetic organic chemistry for the construction of complex carbocyclic as well as heterocyclic compounds[1,2] has created a revolution recently. The versatility of this technology has aroused great interest in developing novel reagents and procedures for the generation of radicals. In addition to various methods, oxidative formation of radicals has attracted a considerable attention in recent years. Amongst various oxidants,[3] ceric ammonium nitrate (CAN) has been extensively used as an oxidant for the generation of carbon radicals.[4,5] Very recently CAN-mediated oxidative addition of ketones and 1,3-diketones to enolacetates,[6] enol silylethers,[7] styrenes[8] and cyclic and acyclic alkenes[9] have been studied extensively. In spite of these investigations, no information is available so far on the CAN-mediated addition of 1,3-diketones to α,β-unsaturated esters. We report here our results on the CAN-mediated regioselective oxidative [3+2] cycloaddition of dimedone and acetylacetone to cinnamic esters to afford 4,5-dihydrofurans stereoselectively and in high yields.

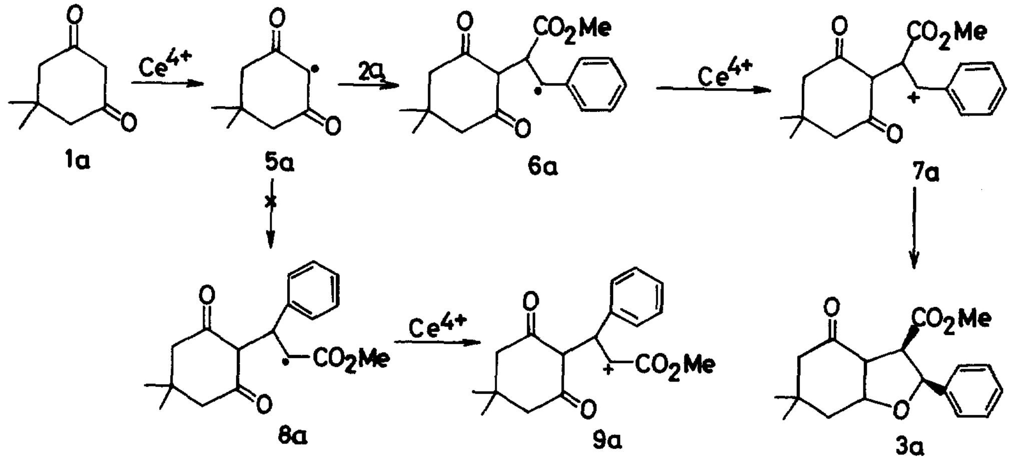
In an illustrative example, as shown in Scheme 1, the treatment of the cinnamic ester **2a** and dimedone **1a** in presence of CAN and $NaHCO_3$ at room temperature afforded the dihydrofuran **3a** in good yield. The reaction was found to be highly regio- and stereoselective, no isomeric product **4a** could be detected. In ^1H NMR spectrum of **3a** the C_1-H appeared as a doublet at 5.85 (J=6 Hz) and the C_2-H appeared as a ddd at 4.0 (J=6,3 and 1.5 Hz). The cis-stereochemistry at C-2 and C-3 in **3a** was assigned by



Scheme 1

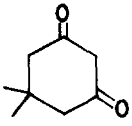
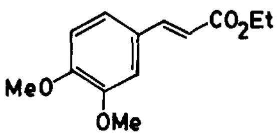
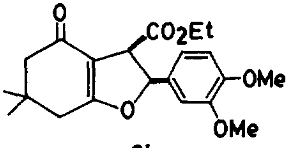
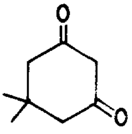
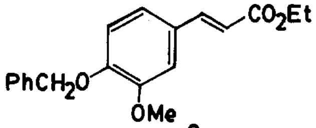
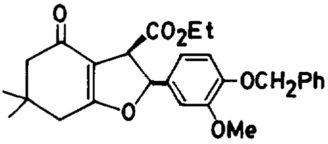
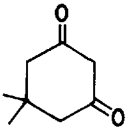
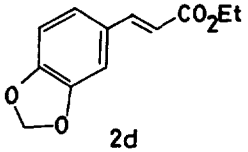
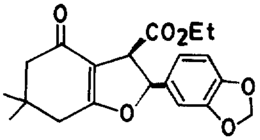
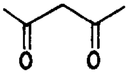
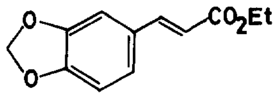
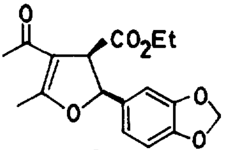
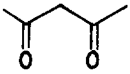
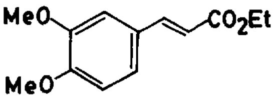
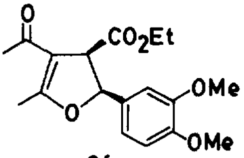
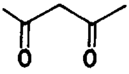
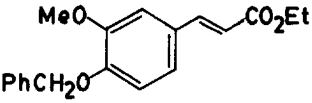
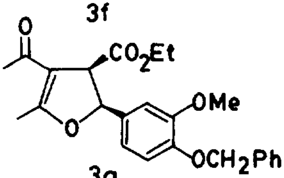
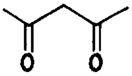
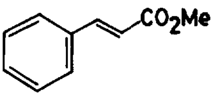
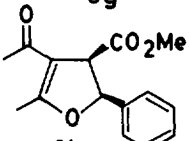
the analogy with the earlier works[9,10] and was further supported by the NOE experiment. Similar results obtained with dimedone and acetylacetone and a number of cinnamic esters are summarised in the Table 1. In all the cases studied here, a minimum of 2.0 equivalents of CAN (with respect to the ester) was required for the completion of the reaction.

Though the exact mechanism of the reaction is still not clear, a rationalisation along the lines shown in Scheme 2 may be made. Since 5a is an electrophilic radical, its low energy SOMO will interact with the highest HOMO of the olefin 2a. The electron withdrawing carboxylic ester group will increase the HOMO coefficient at the α-carbon atom[11] and hence the radical 5a is more likely to react with the olefin at the α-carbon atom with respect to the ester. In separate experiments when methyl acrylate or methyl crotonate was allowed to react with dimedone in



Scheme 2

Table.1 Reactions of 1,3-dicarbonyl compounds with cinnamic esters.

Entry	Dicarbonyl compound	cinnamic ester	product	yield[a] (%)
1	 1a	 2b	 3b	89
2	 1a	 2c	 3c	87
3	 1a	 2d	 3d	87
4	 1b	 2d	 3e	85
5	 1b	 2b	 3f	88
6	 1b	 2c	 3g	86
7	 1b	 2a	 3h	79

[a] Isolated yield.

presence of 2.1 equivalents of CAN, the product was an intractable polymeric material. However, the alternative mechanism which excludes the cation formation cannot be ruled out.

In conclusion, the regio- and stereoselective CAN-mediated oxidative [3+2] cycloaddition of dimedone and acetylacetone to cinnamic esters offers a simple and facile method for the synthesis of tetrasubstituted dihydrofurans. Moreover, the experimental simplicity and high yield of products make this methodology an excellent tool in synthetic organic chemistry.

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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 Brucker AC-200 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 cinnamic ester **2** (1.0 mmol) and the 1,3-diketone **1** (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). The reaction mixture was stirred overnight at room temperature, 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 (25% ethyl acetate in petroleum ether) to afford the pure dihydrofuran **3**.

3-Carbomethoxy-2-phenyl-6,6-dimethyl-2,3,4,5,6,7-hexahydro-1-benzofuran-4-one 3a. m.p. 97-98°C. IR(KBr) ν_{max} 2960, 1735, 1660, 1640, 1500, 1400, 1340, 1310, 1290, 1210, 1170, 1060 cm^{-1}; ^{1}H NMR δ 1.13 (s, 3H), 1.16 (s, 3H), 2.27 (d, J = 2.6 Hz, 2H), 2.43 (d, J = 1.2 Hz, 2H), 3.76 (s, 3H), 4.0 (ddd, J = 6,3 and 1.5 Hz, 1H), 5.85 (d, J = 6 Hz, 1H), 7.24-7.40 (m, 5H). Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found : C, 72.12; H, 6.83.

3-Carbethoxy-2-(3,4-dimethoxy)phenyl-6,6-dimethyl-2,3,4,5,6,7-hexahydro-1-benzofuran-4-one 3b. Viscous oil. IR(neat) ν_{max} 3000, 2860, 1750, 1650, 1530, 1410, 1280, 1180, 1160, 1040 cm^{-1} ; ^{1}H NMR δ 1.12 (s, 3H), 1.15 (s, 3H), 1.26 (t, J = 7 Hz, 3H), 2.27 (d, J = 2.6 Hz, 2H), 2.40 (d, J = 1.8 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.01 (ddd, J = 6, 3.6 and 1.4 Hz, 1H), 4.21 (q, J = 7 Hz, 2H), 5.78 (d, J = 6 Hz, 1H), 6.77 (s, 1H), 6.85 (s, 2H). Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.0. Found : C, 66.98; H, 7.26.

3-Carbethoxy-2-(3-methoxy-4-benzyloxy)phenyl-6,6-dimethyl-2,3,4,5,6,7-hexahydro-1-benzofuran-4-one 3c. Viscous oil. IR(neat) ν_{max} 3000, 2900, 1750, 1650, 1530, 1480, 1420, 1280, 1240, 1040 cm^{-1}; ^1H NMR δ 1.13 (s, 3H), 1.16 (s, 3H), 1.28 (t, J = 7 Hz, 3H), 2.28 (d, J = 2.8 Hz, 2H), 2.32 (d, J = 1.6 Hz, 2H), 3.87 (s, 3H), 4.02 (d, J = 6.2 Hz, 1H), 4.22 (q, J = 7 Hz, 2H), 5.15 (s, 2H), 5.77 (d, J = 6.2 Hz, 1H), 6.67-6.89 (m, 3H), 7.25-7.44 (m, 5H). Anal. Calcd. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found : C, 72.12; H, 7.02.

3-Carbethoxy-2-(3,4-methylenedioxy)phenyl-6,6-dimethyl-2,3,4,5,6,7-hexahydro-1-benzofuran-4-one 3d. Viscous oil. IR(neat) ν_{max} 3000, 2940, 1750, 1650, 1510, 1460, 1420, 1270, 1220, 1120, 1050 cm^{-1}; ^1H NMR δ 1.13 (s, 3H), 1.15 (s, 3H), 1.27 (t, J = 7 Hz, 3H), 2.27 (d, J = 1 Hz, 2H), 2.35 (s, 2H), 3.94 (ddd, J = 6,3 and 1.6 Hz, 1H), 4.21 (q, J = 7 Hz, 2H), 5.73 (d, J = 6 Hz, 1H), 6.0 (s, 2H), 6.73-6.81 (m, 3H). Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found : C, 66.86; H, 6.25.

3-Carbethoxy-2-(3,4-methylenedioxy)phenyl-4-acetyl-5-methyl-2,3,-dihydrofuran 3e. Viscous oil. IR(neat) ν_{max} 2990, 2900, 1735, 1630, 1500, 1490, 1450, 1390, 1250, 1100, 1040 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7 Hz, 3H), 2.25 (s, 3H), 2.35 (d, J = 1.2 Hz, 3H), 3.99 (dd, J = 6 and 1.2 Hz, 1H), 4.24 (q, J = 7 Hz, 2H), 5.54 (d, J = 6 Hz, 1H), 5.97 (s, 2H), 6.79 (s, 3H). Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found : C, 64.52; H, 5.76.

3-Carbethoxy-2-(3,4-dimethoxy)phenyl-4-acetyl-5-methyl-2,3-dihydrofuran 3f. Viscous oil. IR(neat) ν_{max} 2960, 2840, 1740, 1630, 1600, 1510, 1470, 1400, 1270, 1160, 1030 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7 Hz, 3H), 2.25 (s, 3H), 2.35 (d, J = 1 Hz, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.05 (ddd, J = 7,4 and 1.2 Hz, 1H), 4.22 (q, J = 7 Hz, 2H), 5.58 (d, J = 7 Hz, 1H), 6.81-6.86 (m, 3H). Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found : C, 64.80; H, 6.51.

3-Carbethoxy-2-(3-methoxy-4-benzyloxy)phenyl-4-acetyl-5-methyl-2,3-dihydrofuran 3g. Viscous oil. IR(neat) ν_{max} 3020, 2980, 1740, 1640, 1530, 1460, 1280, 1150, 1040, c^{-1}; ^1H NMR δ 1.29 (t, J = 7 Hz, 3H), 2.25 (s, 3H), 2.35 (d, J = 1 Hz, 3H), 3.89 (s, 3H), 4.05 (dd, J = 6 and 1.2 Hz, 1H), 4.23 (q, J = 7 Hz, 2H), 5.15 (s, 2H), 5.58 (d, J = 6 H, 1H), 6.75-6.84 (m, 3H), 7.21-7.44 (m, 5H). Anal. Calcd. for $C_{24}H_{26}O_6$: C, 70.24; H, 6.34. Found : C, 70.06; H, 6.41.

3-Carbomethoxy-2-phenyl-4-acetyl-5-methyl-2,3-dihydrofuran 3h. Viscous oil. IR(neat) ν_{max} 3000, 2980, 1750, 1640, 1450, 1400, 1230, 1100, 1010 cm^{-1}. ^1H NMR δ 2.24 (s, 3H), 2.37 (d, J = 1.4 Hz, 1H), 3.77 (s, 3H), 4.05 (dd, J = 6 and 1.4 Hz, 1H), 5.65 (d, J = 6 Hz, 1H), 7.27-7.39 (m, 5H). Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found : C, 68.87; H, 6.31.

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