Oxidative addition of 1,3-dicarbonyl compounds to dienes mediated by CAN: Formation of dihydrofuran derivatives

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Received 5 November 1999; accepted 1 February 2000

Oxidative addition of 1,3-dicarbonyl compounds to dienes constitutes a facile method for the synthesis of dihydrofuran derivatives.

The generation of C-centered radicals and their addition to a variety of substrates mediated by one electron oxidants such as Mn(III), Co(III) and Ce(IV) reagents have attracted the attention of several research groups recently. A comparative study conducted by us has demonstrated that Ce(IV) ammonium nitrate is superior to the more commonly used Mn(III) acetate in oxidative addition of 1,3-dicarbonyl compounds to unactivated alkenes.

In the context of our recent work in this area, it was of interest to study the oxidative addition of 1,3-dicarbonyl compounds to cyclic and acyclic dienes. It is noteworthy that except for two isolated reports, there has been no effort in the oxidative addition of 1,3-dicarbonyl compounds to dienes. Our preliminary investigations have shown that CAN mediated oxidative addition of 1,3-dicarbonyl compounds like acetyl acetone and dimedone to some cyclic dienes offers an easy route towards the synthesis of dihydrofuran derivatives. The results of our expanded investigations mainly concerned with the addition of radicals to acyclic dienes are reported herein.

Results and Discussion

The present studies were initiated with the oxidative addition of dimedone to different substituted butadienes. The reaction of dimedone with 2,3-dimethylbutadiene in methanolic solution of CAN yielded the dihydrofuran 3 in 70% yield (Scheme I).

The product 3 was purified by chromatography on silica gel column and its structure established by spectral analysis. The α,β-unsaturated carbonyl absorption in the IR spectrum of 3 was observed at 1647 cm⁻¹. In the ¹H NMR spectrum, the signals due to the two olefinic protons appeared at δ 4.98 and 4.48 as singlets. In the ¹³C NMR spectrum the signal due to the carbonyl carbon appeared at δ 194.93. The saturated carbon adjacent to the oxygen in the dihydrofuran ring was visible at δ 93.68.

Dimedone reacted with a variety of dienes to give analogous products. Acetylacetone and ethyl acetacetate were also found to give similar results and these are summarized in Table I.

The configuration of the dihydrofuran derivatives was determined by 2D NMR spectral studies. Compound 14 was taken as a representative example and the ring fusion was assigned as trans based on 2D COSY, NOESY, COLOC and MMX-energy (PC Window-1993) calculation studies.

In the 2D HOMOCOSY spectrum of 14, the ring junction proton (δ 3.20) showed cross peaks with ring junction methyl group (δ 1.50) and the methylene protons at C-9 (δ 2.25) carbon. The NOESY spectrum
Table I—Addition Reactions of 1,3-dicarbonyl compounds to dienes

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<th>Entry No</th>
<th>Dicarbonyl compound</th>
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<th>Product</th>
<th>Yield (%)</th>
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Reaction conditions CAN, MeOH, 0°C, 15-45 min

of 14 did not show any cross peak between ring junction proton and ring junction methyl group. Hence it is assumed that these two are trans to each other. The isopropyl group at C-8 carbon showed cross peaks with ring junction methyl group in NOESY spectrum and hence they are cis to each other. We have taken the phellandrene with R-configuration and hence it implies that C-8 center has R-configuration. Based on these facts, R-configuration was assigned for the C-11 center. It is clear from the NMR spectra that only one double bond is taking part in the reaction and there is no internal shifting of the other one.

The assigned regiochemistry was clear from the $^1$H NMR spectrum. It may be noted that the regiosomer resulting from the reaction with disubstituted double bond would display only one olefinic proton. $^{13}$C NMR spectrum also showed the presence of quaternary carbon adjacent to the dihydrofuran oxygen.

In all the cases studied, two equivalents of CAN were required for the completion of the reaction. If less than two equivalents are used, a proportional amount of diene remained unreacted. Though the mechanistic details of the reaction are not known, a rationalization along the following lines can be given (Scheme II). The first step involves the CAN mediated generation of the radical A from dimedone, which is immediately trapped by the diene giving the intermediate radical B. Subsequently, radical B is oxidized to the cation C by the second equivalent of CAN. The latter then undergoes cyclization to afford the dihydrofuran derivative. The requirement of two equivalents of CAN is in support of the above postulation.

In conclusion, we have developed a novel synthesis of highly substituted dihydrofuran derivatives. In view of the experimental simplicity, it is anticipated that the procedure will find practical applications.
Experimental Section

All experiments were initiated at ice temperature under atmospheric conditions. IR spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra were recorded on the $\delta$ scale with TMS as internal reference using Bruker-300 MHz spectrophotometer. Mass spectra were recorded on a Fisons MD 800 and Hewlett Packard 5890 mass spectrometers. The relative intensities of the m/z values (in percentage) are given in parenthesis.

Purification by gravity column chromatography was done using 100-200 mesh silica gel and appropriate mixture of petroleum ether and ethyl acetate for elution. Commercial grade solvents were used for column chromatography and were distilled before use. Petroleum ether refers to the fraction boiling between 60-80 °C. Analytical thin layer chromatography was performed on glass plates coated with silica gel GF254 containing 13% calcium sulfate as binder.

Relevant spectral data of all the compounds are given. Mass spectral data are given for selected examples.

Synthesis of dihydrofuran derivatives: General procedure. A solution of CAN (1.26 g, 2.3 mmoles) in methanol (10 mL) was added dropwise to an ice cooled, stirred mixture of the dicarbonyl compound (1 mmole) and alkene (1.2 mmoles) in methanol (5 mL). In most of the cases the reddish brown colour of CAN disappeared by the time, the addition was over. (In some isolated cases it took 30-45 min). The mixture after decolourisation was diluted with water (150 mL) and extracted with dichloromethane (5 x 10 mL). The combined organic extracts were washed with water, then with brine, dried over anhydrous sodium sulphate and the solvent was evaporated off. The residue obtained was subjected to chromatography on silica gel column. Elution with 10% ethyl acetate in petroleum ether (unless otherwise specified) afforded the dihydrofuran derivatives.

2, 6, 6-Trimethyl-2-isoprenyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran-4-one 3. IR (CHCl$_3$): 2975, 2935, 2874, 1404, 1249 cm$^{-1}$; $^1\text{H}$ NMR (CDCl$_3$, 300 MHz): $\delta$ 5.59 (m, 5H, ArH), 6.55 (d, 1H, olefinic, J = 16.11 Hz), 6.27 (d, 1H, olefinic, J=16.11 Hz), 2.89 (d, 1H, J=15 Hz), 2.71 (m, 1H, J=15 Hz), 2.28 (s, 2H, CH$_2$), 2.20 (s, 2H, -CH$_2$), 1.57 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$) 1.21 s (3H, CH$_3$); $^{13}\text{C}$ NMR (CDCl$_3$, 75 MHz): $\delta$ 194.94, 175.04, 136.07, 131.9 128.58, 128.38, 127.94, 126.58, 110.96, 91.48, 50.38, 38.22, 37.93, 34.07, 28.64, 28.62, 26.87. Exact mass Calc'd. for C$_{16}$H$_{16}$O$_{2}$ : 282.16155, Found : 282.16188.

2, 6, 6-Trimethyl-2-cinnamyl-2, 3, 4, 5, 6, 7-hexahydrobenzofuran-4-one 12. IR (CHCl$_3$): 2975, 2935, 2874, 1404, 1249 cm$^{-1}$; $^1\text{H}$ NMR (CDCl$_3$, 300 MHz): $\delta$ 5.59 (m, 5H, ArH), 6.55 (d, 1H, olefinic, J = 16.11 Hz), 6.27 (d, 1H, olefinic, J=16.11 Hz), 2.89 (d, 1H, J=15 Hz), 2.71 (m, 1H, J=15 Hz), 2.28 (s, 2H, CH$_2$), 2.20 (s, 2H, -CH$_2$), 1.57 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$) 1.21 s (3H, CH$_3$); $^{13}\text{C}$ NMR (CDCl$_3$, 75 MHz): $\delta$ 194.94, 175.04, 136.07, 131.9 128.58, 128.38, 127.94, 126.58, 110.96, 91.48, 50.38, 38.22, 37.93, 34.07, 28.64, 28.62, 26.87. Exact mass Calc'd. for C$_{16}$H$_{16}$O$_{2}$ : 282.16155, Found : 282.16188.

1-Oxo-8-isopropyl-3, 3, 11-trimethyl-5-oxa-2, 3, 4, 8, 9,10,11-heptahydrofluorene 14. IR (CHCl$_3$): 2980, 2942, 1650, 1450 cm$^{-1}$; $^1\text{H}$ NMR (CDCl$_3$, 300 MHz): $\delta$ 5.92 (d, 1H, olefinic, J = 10.14 Hz), 5.59 (m, 1H, olefinic, J=10.18 Hz), 3.20 (brs, 1H, CH), 2.25 (m, 6H, CH$_2$), 1.81 (brs, 1H, CH), 1.61 (m, 1H, CH), 1.50 (s, 3H, CH$_3$), 1.08 (s, 6H, CH$_3$), 0.89 (brs, 6H,6i-isopropyl); $^{13}\text{C}$ NMR (CDCl$_3$, 75 MHz): $\delta$ 194.82, 175.69, 135.83, 128.725, 113.65, 86.72, 51.25, 43.37, 38.22, 37.72, 31.25, 28.55, 26.05, 19.73, 19.51.

2,5-Dimethyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester 15. IR (CHCl$_3$): 2975, 2935, 1708, 1640, 1452, 1384, 1256 cm$^{-1}$; $^1\text{H}$ NMR CDCl$_3$, 500 MHz): $\delta$ 4.95 (s, 1H, olefinic), 4.79 (s, 1H, olefinic), 4.15 (q, 2H,CH$_2$CH$_3$), 2.88 (d, 1H, CH$_2$J = 14.5 Hz), 2.55 (d, 1H, CH$_3$J = 14.5 Hz), 2.20 (s, 3H, CH$_3$), 1.76 (s, 3H, CH$_3$), 1.44 (s, 3H, CH$_3$), 1.27 (t, 3H, CH$_2$CH$_3$); $^{13}\text{C}$ NMR
2,5-Dimethyl-5-propenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester 16. IR (CH$_2$Cl$_2$): 2985, 2921, 2867, 1701, 1647, 1389, 1236 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 5.57 (m, 1H, olefinic), 4.17 (q, 2H, CH$_2$CH$_3$), 3.22 (d, 1H, CH, J=15.6 Hz), 3.07 (d, 1H, CH, J = 15.2 Hz), 2.18 (s, 3H, CH$_3$), 1.70 (d, 1H, CH$_3$), 1.28 (t, 3H, CH$_3$), 1.20 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 167.39, 166.11, 134.19, 124.21, 101.5, 86.56, 59.05, 41.67, 36.09, 26.18, 17.32, 14.16.

2,5-Dimethyl-5-cinnamyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester 17. IR (CH$_2$Cl$_2$): 2982, 2928, 1742, 1647, 1548, 1378, 1209 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.31 (m, 5H, ArH), 6.55 (d, 1H, olefinic, J = 16 Hz), 6.30 (d, 1H, olefinic, J = 16 Hz), 4.16 (q, 2H, CH$_2$CH$_3$), 2.97 (d, 1H, CH$_2$, J$_1$ = 15 Hz), 2.25 (s, 3H, CH$_3$), 1.56 (s, 3H, CH$_3$), 1.28 (t, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 166.72, 166.47, 136.55, 132.90, 128.77, 127.99, 126.74, 101.36, 87.13, 59.66, 42.41, 27.02, 14.70, 14.58.

2-Methyl-5-propenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester 18. IR (CH$_2$Cl$_2$): 2989, 2928, 2854, 1698, 1384, 1229 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 5.68 (m, 1H, olefinic), 5.57 (m, 1H, olefinic), 4.97 (q, 1H, OCH), 4.16 (q, 2H, CH$_2$CH$_3$), 3.02 (m, 1H, CH$_2$), 2.63 (m, 1H, CH$_2$) 1.5 (s, 3H, CH$_3$), 1.73 (d, 3H, CH$_3$), 1.27 (t, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 167.54, 166.20, 130.17, 129.90, 101.79, 82.97, 59.13, 35.8, 17.63, 14.48, 14.12.

2,5-Dimethyl-5-isopropyl-4,5,8,9-tetrahydrobenzofuran 20. IR (CH$_2$Cl$_2$): 2982, 2928, 1674, 1607, 1384, 1236 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 5.65 (m, 2H, olefinic), 2.89 (d, 1H, CH, J = 15 Hz), 2.73 (d, 1H, CH$_2$, J = 15 Hz), 2.21 (s, 3H, CH$_3$), 2.17 (s, 3H, CH$_3$), 1.71 (d, 3H, CH$_3$), 1.43 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 194.93, 166.71, 134.39, 124.63, 111.73, 87.30, 42.90, 29.60, 26.70, 17.91, 15.53.

Acknowledgements

Authors (LGN and LBG) thank the CSIR, New Delhi for the award of research fellowships and Dr. P Shamumgham and Ms Soumini Mathew for NMR Spectra.
References


