Synthesis of some dihydropyran derivatives by utilizing crotonoyl cyanides as heterodienes in a very mild condition

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Received 7 December 1999; accepted (revised) 8 September 2000

The reaction of crotonoyl cyanide 1 and its bromo derivative 2 with trimethylene 3 affords the dihydropyran 6 and 7, respectively. Similarly the compound 1 on reaction with acrolein dimethyl acetal 4 and acrolein diethyl acetal 5 gave the isomeric products 8a/8b and 9a/9b, respectively; the cis-isomer being the predominant one. On the other hand the bromo derivative 2 on treatment with the compound 5 yields only the cis-isomer 10. BF3·Et2O catalysed epimerisation of 11a gives the other epimer 11b in a mild condition with reasonable yield.

Hetero-Diels-Alder reaction with inverse electron demand is a most important synthetic method for the synthesis of functionally substituted tetrahydropyran derivatives. Hetero-Diels-Alder reactions of α,β-unsaturated carbonyl compounds as heterodienes are well known. The introduction of electron withdrawing groups at the α- or β-position of the α,β-unsaturated carbonyl compounds increase the reactivity of such a heterodiene in the inverse Diels-Alder reactions. The acryloyl cyanides react at room temperature with excess enol ether to give the dihydropyran mostly in high yields, the cis-isomer being the major product. The enhanced reactivity is also reported for 2-cyano-1-azadiene and bromosubstituted crotonoyl cyanides. In continuation of our investigation for the synthesis of new 3,4-dihydro-2H-pyran-6-carbonitrile derivatives we have used crotonyl cyanide 1 and 3-bromo-2-oxopent-3-en nitrile 2 as heterodienes and trimethyl ethene 3, acrolein dimethyl acetal 4 and acrolein diethyl acetal 5 as dienophiles. We also report herein an epimerisation of cis-isomer to trans-isomer under mild conditions.

Results and Discussion

In our present study we have synthesized functionally substituted dihydropyran derivatives by the inverse type Hetero-Diels-Alder reaction. The heterodienes 1 and 2 used in these reactions were prepared from the commercially available crotonic acid in three steps. The dienophiles 3,4 and 5 were purchased from Aldrich Chemical Company.

The reaction of crotonoyl cyanide 1 with trimethyl ethene 3 at room temperature for 6 days afforded the product 6 as a pale yellow liquid in 93% yield (Scheme I). The presence of the ν(C=N) group at 2240 cm\(^{-1}\) and the absence of ν(C=O) group in the IR spectra indicated the formation of the product. In the \(^1\)H NMR spectra it showed four distinct methyl signals at \(\delta\) 1.24(s), 1.24(s), 1.3 (d, \(J=6.5\) Hz) and 1.90 (d, \(J=7.0\) Hz). The signals for 3-H and 4-H are shown at \(\delta\) 2.62(dq)
and at δ 2.85 (ddq), respectively. The olefinic proton is at δ 7.0 (d) together with the other signals in the 1H NMR clearly proved the structure of 6 as 6-cyano-2,2,3,4-tetramethyl-3,4-2H-pyran. The mass spectrum fragmentation of 6 further proved its structure. The heterodiene 2 on reaction with 3 at room temperature for 4 days gave the compound 7 in 72% yield. The presence of νCN at 2234 cm⁻¹ and νCC at 1654 cm⁻¹ and the absence of νCS in IR spectra showed the formation of the compound 7. 1H NMR spectrum of 7 gave distinct signals for different protons. The four methyl protons appeared at δ 0.9 (d, J=6 Hz), 1.20 (d, J=7 Hz), 1.28 (s) and 1.32 (s). The 3-H and 4-H are shown by the absorption at δ 1.95 (dq) and at δ 2.79 (dq), respectively. The mass spectrum showed the molecular ion peak at m/z 243/245 with bromine isotopic pattern and confirmed the structure for 7 as 5-bromo-6-cyano-2,2,3,4-tetramethyl-3,4-dihydro-2H-pyran. No stereo-isomer is possible for the compound 6 and 7.

The reaction of crotonoyl cyanide 1 and acrolein dimethyl acetal 4 carried out at room temperature for 10 days or by refluxing their mixture for 5 hrs resulted in the formation of two isomeric products 8a and 8b in 36% yield. Both 8a and 8b showed the presence of νCN and νCC group in the IR spectra. Both the compounds 8a and 8b showed all the proton signals in the 1H NMR spectrum. In the crude mixture the intensity of the peaks differ distinctly in the 1H NMR. Moreover the structural feature is decided by the coupling constants of 2-H proton with the adjacent 3-H protons and the CH₂⁻O proton. The coupling constants for 2-H in 8b are very much smaller than the 2-H in 8a. The smaller couplings indicate its position as equatorial in 8b compared to axial position in 8a. The ion peak at 196 (M⁺-1) and other fragmentation pattern in the mass spectra confirmed the structures for 8a and 8b, as cis- and trans-2-dimethoxymethyl-4-methyl-6-cyano-3,4-dihydro-2H-pyran, respectively.

Similarly the reaction of crotonoyl cyanide 1 with acrolein diethyl acetal 5 for 10 days at room temperature afforded the two isomeric products 9a and 9b in 34% yield. Both 9a and 9b also showed the presence of νCN and νCC groups and absence of νCS group in the IR spectra. In the 1H NMR spectra the two isomers 9a and 9b showed distinct peaks, the intensity of the peaks differ in the ratio of 2:1, respectively. The structural assignment is also proved by the coupling constants of 2-H proton with the 3-H protons and CH₂⁻O proton. The 2-H proton of 9a showed a larger couplings (J=4.9 Hz) with both the 3-H proton and CH₂⁻O proton. Whereas 2-H of 9b showed a coupling of (J=2.67 and 1.24 Hz) with 3-H proton and CH₂⁻O proton. The smaller coupling of 1.2 Hz clearly indicates its position as equatorial compared to axial position of 2-H in 9a. In mass spectra both the compounds showed the molecular ion peak at 225 (M⁺) consistent with the molecular formula C12H19O3N and the given structures cis- and trans-2-diethoxymethyl-4-methyl-6-cyano-3,4-dihydro-2H-pyran for 9a and 9b, respectively.

On the other hand from the reaction of 2 with acrolein diethyl acetal 5 at room temperature for 8 days afforded only single cis-isomer 10; the other isomer could not be isolated. The yield of 10 was 70%. The compound 10 also showed νCN and νCC bands at 2275 cm⁻¹ and at 1635 cm⁻¹ respectively in the IR spectra. 1H NMR spectrum of 10 showed the distinct signals for different protons. The compound 10 showed three methyl signals at δ 0.9 (t), 1.21 (t) and 1.26 (d). The significant 2-H proton is at δ 4.70(m); the coupling constants are 2.5 and 5 Hz with the 3-H protons and the CH₂⁻O proton is at δ 5.40 (d, J=4.7 Hz). The mass spectra showed the different fragmentations suited to the given structure 2-diethoxymethyl-4-methyl-5-bromo-6-cyano-3,4-dihydro-2H-pyran for 10. The structure for the isolated compound 10 was assigned as cis-isomer.

Epimerization of 11a with BF₃·Et₂O at room temperature for 1 hr gave the product 11b. The epimer 11b showed the characteristic bands as in 11a in the IR spectra. 1H NMR of the compound 11b gave two doublets with very small coupling constants J=1.5 Hz and J=1 Hz, at δ 5.62 and 5.05 for the olefinic 5-H and 2-Hp, respectively. The compound 11a showed a larger axial coupling (J=6.5 Hz) for 2-Hα proton indicating its position as axial. The spectral data confirmed the structure of 11b as trans-butoxy-4-methyl-6-cyano-3,4-dihydro-2H-pyran. The mass spectrum also confirmed this structure.
Experimental Section

General. Melting points were recorded by thin disc method on a Fischer Johns electrothermal melting point apparatus and are uncorrected. IR spectra were recorded in nujol mull or as solution in CCl₄ as an evaporated film using DR 8001 Shimadzo FT-IR spectrometer; ¹H NMR spectra in CDCl₃ on a Bruker WH 400 MHz spectrometer with TMS as internal standard and mass spectra on a Varian MAT 711 (70 ev) spectrometer and on Varian MAT 44S spectrometer with GC combination.

Synthesis of 6-cyano-2,2,3,4-tetramethyl-3,4-dihydro-2H-pyran 6. To crotonyl cyanide¹⁰ ¹ (0.285 g, 3 mmoles), 3.2 mL of trimethylethene ³ (2.1 g, 30 mmoles) was added taken in a three-necked round bottom flask drop by drop with stirring at room temperature. The stirring was continued for 6 days at this temperature for completion of the reaction. The excess trimethylethene ³ was removed in a rotatory evaporator under reduced pressure when a yellowish crude liquid (0.48 g) was obtained. The crude product was column chromatographed in a silica-gel (60-120 mesh) column eluting with n-hexane:dichloromethane (4:1) as eluent when the pure product 6 was obtained. The Rₐ of 6 was 0.58 (n-hexane:dichloromethane:1:2) and the yield was 0.46g (93%). The spectroscopic data are given in Table I.

Synthesis of 5-bromo-6-cyano-2,2,3,4-tetramethyl-3,4-dihydro-2H-pyran 7. 3.2 mL of trimethylethene ³ (2.1 g, 30 mmoles) was added dropwise to 3-bromo-2-oxo-pent-3-en nitrile¹⁰ ² (0.51g, 3 mmoles) with continuous stirring at room temperature. The stirring was continued for further 4 days until completion of the reaction. The excess trimethylethene ³ was removed in a rotatory evaporator under reduced pressure. The yellowish crude (0.56g) was chromatographed on a silica-gel column eluting first with cyclohexane and then with cyclohexane:dichloromethane (99:1) solvent mixture to get the product. The product thus obtained was again chromatographed with the same solvent when 260 mg (36%) of the products 8a and 8b were isolated. ¹H NMR spectra showed the ratio of 8a to 8b to be 2:1. The spectral data are given in Table I.

Synthesis of cis- and trans-2-diethoxymethyl-4-methyl-6-cyano-3,4-dihydro-2H-pyran (9a and 9b). 2.5 mL of acrolein diethyl acetal ⁵ (2.1 g, 16 mmoles) was added dropwise to 0.5g of crotonyl cyanide ¹ (5.26 mmoles) at room temperature with stirring. The reaction mixture was stirred for 10 days at this temperature. Excess acrolein diethyl acetal was removed in a rota-evaporator under reduced pressure. The crude liquid (1.19g) was chromatographed on a silica-gel column first with cyclohexane and then with cyclohexanemethyl acetate (99:1) solvent mixture to get the product. The product thus obtained was again chromatographed with the same solvent when 350 mg (34%) of the products 9a and 9b were isolated. The ¹H NMR spectra showed it to be a mixture in the ratio 2:1. The spectroscopic data are given in Table I.

Synthesis of cis-2-diethoxymethyl-4-methyl-5-bromo-6-cyano-3,4-dihydro-2H-pyran 10. To 3-bromo-2-oxopent-3-en nitrile ² (0.52g, 3 mmoles) was added dropwise 2.5 mL of acrolein diethyl acetal ⁵ (2.1 g, 16 mmoles) with stirring at room temperature. The reaction was continued for 8 days at this temperature. Excess acrolein diethyl acetal was removed in a rota-evaporator under reduced pressure. The reddish crude liquid (1.01g) was chromatographed on a silica-gel column using petroleum ether (bp 40-60°C): ethyl acetate (9.8:0.2) solvent system. After chromatography 590 mg (70%) of the pure product 10 was isolated. The spectroscopic data are given in Table I.

Epimerisation of cis-2-butoxy-4-methyl-6-cyano-3,4-dihydro-2H-pyran 11a by treatment with BF₃·ET₂O. To a solution of 11a (0.5g, 2.5 mmoles) in 10 mL CH₂Cl₂ was added dropwise BF₃·ET₂O (0.26 mL, 2 mmoles) at room temperature and stirred for 1 hr. The reaction mixture was quenched with brine solution and the organic phase was separated, dried over anhydrous Na₂SO₄ and the solvent removed in vacuum when a mixture of starting product 11a and the epimeric trans-product 11b was obtained. The crude product (0.4g) on column chromatographic
### Table I — Spectroscopic data of the synthesized compounds

<table>
<thead>
<tr>
<th>Compd</th>
<th>$^1$H NMR</th>
<th>MS</th>
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<tbody>
<tr>
<td>6</td>
<td>1.2 (s, 3H, 2-Me), 1.24 (s, 3H, 2-Me), 1.30 (d, 3H, $J$=6.5 Hz, 4-Me), 1.90 (d, 3H, $J$=7.0 Hz, 3-Me), 2.62 (dq, 1H, $J$=4.5, 7 Hz, 3-H), 2.85 (ddq, 1H, $J$=4.0, 4.5, 6.5 Hz, 4-H), 7.0 (dd, $J$=4.0, 1 Hz, 5-H)</td>
<td>163 (M$^+$-2H, 19%), 148 (M$^+$-2H-Me, 24), 135 (M$^+$-2H-CO, 20), 120 (M$^+$-2H-COMe, 76), 109 (M$^+$-2H-COCN, 12), 93 (M$^+$-2H-Me-C$_2$H$_4$, 4), 92 (M$^+$-2H-Me-C$_3$H$_4$, 23), 68 (100).</td>
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<td>7</td>
<td>0.9 (d, 3H, $J$=6.0 Hz, 4-Me), 1.2 (d, 3H, $J$=7.0 Hz, 3-Me), 1.28 (s, 3H, 2-Me), 1.32 (s, 3H, 2-Me), 1.95 (dq, 1H, $J$=4.0, 7.0 Hz, 3-H), 2.79 (dq, 1H, $J$=4.0, 6.0 Hz, 4-H)</td>
<td>243, 245 (M$^+$, bromine isotopic pattern, 1%), 200, 202 (M$^+$-HCN-CH$_2$, &lt;1), 186, 188 (M$^+$-CN-2xCH$_3$, &lt;1), 164 (M$^+$-Br, 1), 149 (M$^+$-Br-CH$_3$, 1), 134 (M$^+$-Br-2xCH$_3$, 1), 121 (M$^+$-Br-CO, 2), 70(100).</td>
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<tr>
<td>8a</td>
<td>1.13 (d, 3H, $J$=7.3 Hz, 4-Me), 1.80 (m, 1H, 3-H), 2.37 (m, 1H, 3-H), 2.70 (m, 1H, 4-H), 3.32 (s, 3H, OCH$_3$), 3.53 (s, 3H, OCH$_3$), 4.20 (ddd, 1H, $J$=2.5, 4.7, 5 Hz, 2-H), 4.90 (d, 1H, $J$=4.7 Hz, CH$_2$),</td>
<td>196 (M$^+$-H, 1%), 167 (M$^+$-2CH$_3$, 80), 149 (M$^+$-OH-OMe, 100), 122 (M$^+$-CH(OH)Me), 3, 121 (M$^+$-OH-OH-OMe-CH$_2$N, 5), 94 (M$^+$-CH(OH)Me)$_2$-HCN, 5).</td>
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<tr>
<td>8b</td>
<td>1.14 (d, 3H, $J$=7 Hz, 4-CH$_3$), 1.60 (m, 1H, 3-H), 2.30 (m, 1H, 3-H), 2.80 (m, 1H, 4-H), 3.32 (s, 3H, OMe), 3.52 (s, 3H, OMe), 4.20 (ddd, 1H, $J$=2.5, 3.0, 3.7 Hz, 2-H), 5.63 (d, 1H, $J$=3.0 Hz, 4-CH$_3$),</td>
<td>196 (M$^+$-H, 1%), 167 (M$^+$-2CH$_3$, 80), 149 (M$^+$-OH-OMe, 100), 122 (M$^+$-CH(OH)Me)$_2$, 3, 121 (M$^+$-OH-OH-OMe-CH$_2$N, 5), 94 (M$^+$-CH(OH)Me)$_2$-HCN, 5).</td>
</tr>
<tr>
<td>9a</td>
<td>1.17 (d, 3H, $J$=6.9 Hz, 4-CH$_3$), 1.15 (t, 3H, $J$=6.9 Hz, OCH$_2$CH$_3$), 1.20 (t, 3H, $J$=7.3 Hz, OCH$_2$CH$_3$), 1.80 (m, 1H, 3-H), 2.36 (m, 1H, 3-H), 2.78 (m, 1H, 4-H), 3.40 (dq, 1H, $J$=10, 7.3 Hz, OCH$_2$CH$_3$, 3.57 (dq, 1H, $J$=10, 7.3 Hz, OCH$_2$CH$_3$), 3.86 (dq, 1H, $J$=10, 6.9 Hz, OCH$_3$), 4.20 (dq, 1H, $J$=10, 6.9 Hz, OCH$_3$), 5.10 (ddd, 1H, $J$=2.6, 6.9 Hz, 2-H), 5.61 (d, 1H, $J$=4.9 Hz, CH$_2$),</td>
<td>225 (M$^+$, 4%), 197 (M$^+$-HCN, 1), 196 (M$^+$-Et, 2), 179 (M$^+$-EtOH, 10), 166 (M$^+$-Et-2xMe, 26), 151 (M$^+$-HCN-EtOH, 12), 140 (M$^+$-Et-2xCH$_3$, –CN$, 4), 135 (M$^+$-2xOEt, 18), 122 (M$^+$-CH(OEt)$_2$, 10), 86 (100).</td>
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<td>9b</td>
<td>0.88 (t, 3H, $J$=6.3 Hz, OCH$_2$CH$_3$), 1.01 (d, 3H, $J$=6.4 Hz, 4-CH$_3$), 1.16 (t, 3H, $J$=7 Hz, OCH$_2$CH$_3$), 1.40 (m, 1H, 3-H), 1.65 (m, 1H, 3-H), 2.38 (m, 1H, 4-H), 3.44 (dq, 1H, $J$=10.5, 7 Hz, OCH$_2$CH$_3$, 3.59 (dq, 1H, $J$=10, 7 Hz, OCH$_2$CH$_3$), 3.85 (dq, 1H, $J$=10, 6.3 Hz, OCH$_3$), 4.20 (dq, 1H, $J$=10, 6.3 Hz, OCH$_3$), 5.15 (ddd, 1H, $J$=2.4, 2.67, 4.7 Hz, 2-H), 5.51 (d, 1H, $J$=4.7 Hz, CH$_2$),</td>
<td>225 (M$^+$, 4%), 197 (M$^+$-HCN, 1), 196 (M$^+$-Et, 2), 179 (M$^+$-EtOH, 18), 166 (M$^+$-Et-2xCH$_3$, 26), 151 (M$^+$-HCN-EtOH, 15), 149 (M$^+$-EtOH-2xCH$_3$, 40), 120 (50), 86 (100).</td>
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<td>10</td>
<td>1.1 (t, 3H, OCH$_2$CH$_3$), 1.21 (t, 3H, OCH$_2$CH$_3$), 1.26 (d, 3H, 4-CH$_3$), 1.60 (m, 1H, 3-H), 1.75 (m, 1H, 3-H), 1.90 (m, 1H, 4-H), 3.45 (dq, 1H, OCH$_3$), 3.56 (dq, 1H, OCH$_3$), 3.60 (dq, 1H, OCH$_3$), 3.70 (dq, 1H, OCH$_3$), 4.70 (ddd, 1H, $J$=2.5, 4.7, 5 Hz, 2-H), 5.40 (d, 1H, $J$=4.7 Hz, CH$_2$),</td>
<td>258, 260 (M$^+$-OEt, bromine isotopic pattern, 1), 243, 245 (M$^+$-OEt-CH$_3$, 3), 223 (M$^+$-HBr, 4), 165 (M$^+$-HBr-2Et, 18), 149 (M$^+$-HBr-2EtOEt, 20), 111 (30), 103 (100), 85 (100), 57 (100).</td>
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<tr>
<td>11b</td>
<td>0.92 (t, 3H, ethereal CH$_3$), 1.18 (d, 3H, 4-CH$_3$), 1.20-1.45 (m, 2H, CH$_2$), 1.45-1.80 (m, 3H, CH$_3$), 1.95 (dd, 1H, 3-H, 2.10 (dd, 1H, 3-H), 2.60 (m, 1H, 4-H), 3.49 (dt, 1H, OCH$_3$), 3.86 (dt, 1H, OCH$_3$), 5.05 (t, 1H, $J$=1 Hz, 2-H), 5.62 (d, 1H, $J$=1.5 Hz, 5-H),</td>
<td>196 (M$^+$+1.5), 12 (M$^+$-BuOH, 30), 95 (M$^+$-BuOH-CN, 30), 85 (70), 69 (30), 56 (100).</td>
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</table>
separation on a silica-gel column with n-hexane gave two pure fractions, one was the epimeric trans-product 11b (0.2g, 50%) and the other was the starting cis-product 11a (0.1g). The spectral data are given in Table I.

Acknowledgement
The authors are thankful to Elias Molla, Institute of Inorganic Chemistry, Bayreut University, Germany and to Nurul Abser, Department of Chemistry, University of Sheffield, U.K. for recording the spectra of the compounds.

References