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CYCLOADDITION REACTIONS OF ACYL KETENES WITH ENOL ETHERS: A GENERAL SYNTHESIS OF 2-ALKOXY-2,3-DIHYDRO-4H-PYRAN-4-ONES.

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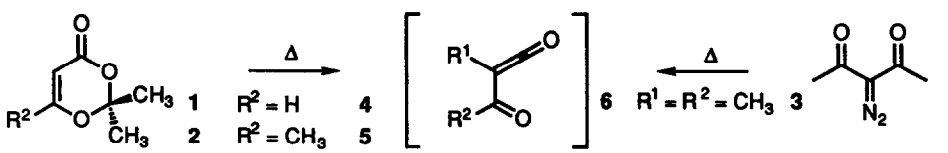
Summary: A detailed description of the hetero Diels-Alder reactions of acyl ketenes **4-6** with electron-rich dienophiles **7-9** for the facile synthesis of 2-alkoxy-2,3-dihydro-4H-pyran-4-ones **10-12** is presented.

Recent developments in carbohydrate biochemistry have delineated the crucial role that oligosaccharides play at the interface of cell-cell recognition and immunochemical events.[2] Of considerable importance is the modulation of biological properties of cells by incorporation of complex carbohydrates into cellular biooligomers (*i.e.*, glycoconjugates), thereby influencing the physical properties, antigenic characteristics, and membrane binding capacity of cells.[3] Concurrent efforts in synthetic chemistry have encompassed the development of effective, stereocontrolled methods for the partial and *de novo* synthesis of simple and complex carbohydrates.[4] Of particular relevance to this work are the recent advances describing the use of [4+2] cycloaddition reactions for the construction of pyranoid ring systems.[5]

1-Oxabutadienes exhibit excellent and predictable regioselectivity in [4+2] cycloaddition reactions, and as electron-deficient dienes they participate preferentially in inverse ($LUMO_{diene}$ controlled) Diels-Alder reactions with electron-rich dienophiles.[5a] Acyl ketenes readily react as the 4π component in [4+2] cycloadditions with a variety of hetero-, olefinic, and acetylenic dienophiles,[6] although their utilization for the construction of pyran systems of relevance to carbohydrate total synthesis has not been detailed to date.[6d] Herein, we describe a potentially versatile approach to the 2-alkoxy-2,3-dihydro-4H-pyran-4-one ring system that is based on the [4+2] cyclocondensation of electron-deficient acyl ketenes with electron-rich enol ethers and ketene acetals (Equation 1).

Equation 1

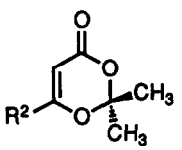
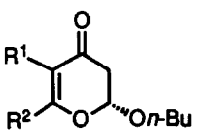
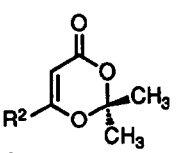
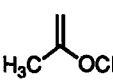
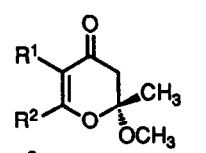
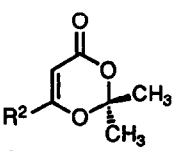
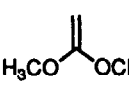
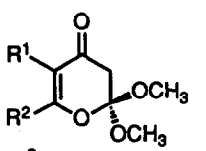
Acyl ketenes **4** and **5** were thermally generated[6b,c] from dioxenones **1**[7a] and **2**,[7b] respectively, whereas acyl ketene **6** was generated by the thermal rearrangement[6a] of 3-diazo-2,4-pentanedione[7c] (**3**, Equation 2). In the studies described herein, acyl ketenes **4-6** were formed by the addition of toluene solutions of precursors **1-3**, respectively, to a refluxing toluene solution of the corresponding dienophile.



Equation 2

The results of our preliminary studies on the cyclocondensation of acyl ketenes **4-6**, generated *in situ* from **1-3**, respectively, with the representative electron-rich olefins butyl vinyl ether (**7**), 2-methoxypropene (**8**), and 1,1-dimethoxyethylene (**9**), are presented in the Table. The reactions were performed by the dropwise addition (2 h, syringe pump) of a dry toluene solution of **1-3** (1 equiv) to a refluxing solution of dienophiles **7-9** (5 equiv) in dry toluene under N_2. After an additional 30 min at reflux, the reaction mixtures were cooled, concentrated *in vacuo*, and the products **10-12**[8] were isolated by bulb-to-bulb distillation. Slow addition (2 h) of the acyl ketene precursors **1-3** to the reaction mixture effectively prevented the formation of dimeric products arising from self-condensation of the intermediate acyl ketenes.[6]

TABLE ***Cyclocondensation Reactions of Acyl Ketenes with Electron-Rich Olefins***

Entry	Acyl Ketene Precursor	Dienophile (Conditions)	Product[e]	Yield (%)[f]
1	 $R^2 = H$[a] (**1**)	 (**7**)[c]	 $R^1 = R^2 = H$ (**10a**)	70
2	$R^2 = Me$[b] (**2**)	5 equiv, toluene, 110°C, 2.5 h	$R^1 = H, R^2 = Me$ (**10b**)	84
3	3-diazo-2,4-pentanedione (**3**)		$R^1 = R^2 = Me$ (**10c**)	64
4	 $R^2 = H$[a] (**1**)	 (**8**)[c]	 $R^1 = R^2 = H$ (**11a**)	48
5	$R^2 = Me$[b] (**2**)	5 equiv, 0.15 equiv 2,6-lutidine, toluene, 110°C, 2.5 h	$R^1 = H, R^2 = Me$ (**11b**)	50
6	3-diazo-2,4-pentanedione (**3**)		$R^1 = R^2 = Me$ (**11c**)	50
7	 $R^2 = H$[a] (**1**)	 (**9**)[d]	 $R^1 = R^2 = H$ (**12a**)	64
8	$R^2 = Me$[b] (**2**)	5 equiv, 0.15 equiv 2,6-lutidine or Reillex™ 402, toluene, 110°C, 2.5 h	$R^1 = H, R^2 = Me$ (**12b**)	94
9	3-diazo-2,4-pentanedione (**3**)		$R^1 = R^2 = Me$ (**12c**)	87

[a]Prepared according to ref. 7a. [b]Available from Lancaster Organics, Ltd. [c]Available from Aldrich Chemical Co. [d]Available from Wiley Organics. [e]All new compounds exhibited satisfactory spectral data (^1H and ^{13}C NMR, IR, EIMS, HRMS) consistent with the indicated structure.[8] [f]Yields for entries 8-9 refer to reactions run with Reillex™ 402 poly(4-vinylpyridine) as acid scavenger; yields for entries 4-6 were determined by ^1H NMR (CH_2Br_2 internal standard); all other yields refer to isolated, distilled products.

Reactions 4-6 and 7-9 were performed in the presence of catalytic (0.15 equiv) 2,6-lutidine or Reillex™ 402 poly(4-vinylpyridine), thereby markedly increasing the isolated yield of 2,3-dihydro-4H-pyran-4-one products by suppressing the formation of γ-pyrone byproducts resulting from acid-promoted elimination of the 2-alkoxy group of **11** and **12**. While the presence of base effectively prevented this elimination during the cycloaddition reactions of acyl ketenes **4-6** with 2-methoxypropene (entries 4-6), a significant amount of thermal elimination was observed during subsequent distillation, thereby complicating product purification. Surprisingly, compounds **11a-11c** existed as a *ca.* 2.5:1 mixture of enol/keto tautomers[9] in $CDCl_3$ (25°C) and this ratio increased to 4.4:1 for **11b** in CD_3OD (25°C), as determined by ^1H NMR. The origin of this phenomenon is unclear[9] and was not observed with compounds **10a-10c** or **12a-12b**, which existed exclusively as the keto tautomers, as evidenced by ^1H NMR ($CDCl_3$). Reaction of acyl ketene precursors **1-3** with 3,4-dihydro-2H-pyran and 2,3-dihydrofuran failed to provide the desired pyrano[2,3-*b*]pyran and furano[2,3-*b*]pyran cycloaddition products.[6d] Instead, products were observed that appeared to arise from simple attack by the enol ether on the ketene moiety without subsequent cyclization.

The methodology described in this communication allows for the simple, one-step construction of 2-alkoxy-2,3-dihydro-4H-pyran-4-one systems that are accessible intermediates for the total synthesis of biologically important 2,6-dideoxy hexopyranose sugars (*cf.* compound **10b**, entry 2). Furthermore, the capability to construct potential ketose sugar precursors such as **11a** and **11b** (*cf.* entries 4 and 5) portends the eventual application of this methodology to the synthesis of higher-order monosaccharides.

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1. Camille and Henry Dreyfus Foundation Distinguished New Faculty Awardee, 1989.

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8. **2-(1-Butoxy)-6-methyl-2,3-dihydro-4H-pyran-4-one (10b).** A solution of **1**[7a] (142 mg, 1.0 mmol) in dry toluene (5 mL) was added *via* syringe pump over a 2 h period to a refluxing solution of butyl vinyl ether (0.46 mL, 5 mmol, 5 equiv) in dry toluene (27 mL). The reaction mixture was warmed at reflux for an additional 30 min and was then cooled to room temperature. The toluene was removed *in vacuo* to give a yellow oil, which was purified by bulb-to-bulb distillation (bp 60°C, 1.2 mm Hg) to afford **10b** (154 mg, 184 mg theor., 84%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (dd, J = 5.8, 3.9 Hz, 1H, C*H*O(O*n*-Bu)), 5.30 (s, 1H, C=C*H*), 3.79 (m, 1H, OC*H*H), 3.52 (m, 1H, OCH*H*), 2.63 (dd, J = 16.7, 3.9 Hz, 1H, C(=O)CHH), 2.51 (dd, J = 16.7, 5.8Hz, 1H, C(=O)CH*H*), 1.95 (s, 3H, C=CCH_3), 1.53 (m, 2H, OCH$_2$CH_2), 1.32 (m, 2H, CH_2CH$_3$), 0.85 (t, J = 7.3 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.47 (C-4), 170.94 (C-6), 105.69 (C-5), 101.98 (C-2), 69.80, 41.96 (C-3), 31.85, 25.38, 21.39, 19.49, 14.11; IR (neat) ν_{max} 3000, 1738, 1640, 1392, 1370, 1272, 1205, 1031, 1007, 901, 805 cm^{-1}; EIMS, *m/e* (relative intensity) 184 (M$^+$, 50), 168 (8), 126 (18), 127 (20), 113 (45), 111 (base), 100 (20), 85 (85), 71 (50), 68 (32), 57 (75), 56 (90); HRMS, *m/e* calcd for $C_{10}H_{16}O_3$: 184.1099; found: 184.1098.

2-(1-Butoxy)-5,6-dimethyl-2,3-dihydro-4H-pyran-4-one (10c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (dd, J = 6.3, 3.9 Hz, 1H, OC*H*(O*n*-Bu)), 3.80 (m, 1H, OC*H*H), 3.52 (m, 1H, OCH*H*), 2.69 (dd, J = 16.7, 3.9 Hz, 1H, C(=O)C*H*H), 2.58 (dd, J = 16.7, 6.3 Hz, 1H, C(=O)CH*H*), 2.00 (s, 3H, C=CCH_3), 1.69 (s, 3H, C=CCH_3), 1.55 (m, 2H, OCH$_2$CH_2), 1.33 (m, 2H, CH_2CH$_3$), 0.89 (t, J = 7.3 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.01 (C-4), 165.84 (C-6), 110.75 (C-5), 100.51 (C-2), 69.15, 41.78 (C-3), 31.46, 19.10, 17.98, 13.80, 9.34; IR (neat) ν_{max} 2930, 2360, 2340, 1731, 1665, 1622, 1394, 1341, 1146, 1097, 1017, 895, 668 cm^{-1}; EIMS, *m/e* (relative intensity) 198 (M$^+$, 50), 155 (5), 141 (20), 127 (30), 125 (base), 99 (57), 85 (40), 71 (32), 57 (50), 56 (78); HRMS, *m/e* calcd for $C_{11}H_{18}O_3$: 198.1256; found: 198.1253.

2,6-Dimethyl-2-methoxy-2,3-dihydro-4H-pyran-4-one (11b). ^{1}H NMR (300 MHz, $CDCl_3$) δ (enol) 13.83 (br s, 1H, OH), 5.36 (s, 1H, C=C*H*), 5.05 (s, 1H, C=C*H*), 3.63 (s, 3H, OCH$_3$), 2.31 (s, 3H, CH$_3$), 1.99 (s, 3H, CH$_3$); δ (keto) 5.44 (s, 1H, C=C*H*), 3.64 (s, 3H, OCH$_3$), 3.53 (s, 2H, C(=O)CH_2), 2.28 (s, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$); EIMS, *m/e* (relative intensity) 156 (M$^+$, 45), 141 (50), 125 (80), 124 (40), 99 (base), 85 (50), 72 (63), 69 (47), 59 (35); HRMS, *m/e* calcd for $C_8H_{12}O_3$: 156.0786; found: 156.0789.

2,2-Dimethoxy-2,3-dihydro-4H-pyran-4-one (12a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 6.2 Hz, 1H, OC*H*=CH), 5.41 (d, J = 6.2 Hz, 1H, OCH=C*H*), 3.30 (s, 6H, OCH$_3$), 2.78 (s, 2H, C(=O)CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.45 (C-4), 158.67 (C-6), 116.54 (C-5), 107.21 (C-2), 50.24, 43.45 (C-3); IR (neat) ν_{max} 2951, 1685, 1607, 1402, 1284, 1244, 1110, 997, 894, 787 cm^{-1}; EIMS, *m/e* (relative intensity) 158 (M$^+$, 3), 143 (9), 128 (43), 127 (70), 101 (10), 88 (88), 85 (30), 72 (15), 69 (30), 58 (72), 57 (base), 54 (10); HRMS, *m/e* calcd for $C_7H_{10}O_4$: 158.0579; found: 158.0582.

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