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Alkylative Carbonyl Transposition of Dihydro-γ-pyrones to Dihydro-α-pyrones#

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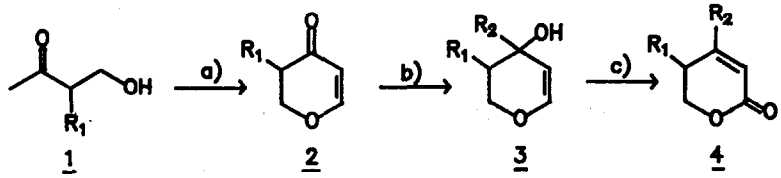
Abstract: Dihydro-γ-pyrones (2) are prepared from β-hydroxy ketones (1). Dihydropyrones (2) are transformed to unsaturated δ-lactones (4) via an alkylative 1,3-carbonyl transposition.

There has been increasing interest in the chemistry of substituted 2,3-dihydro-4H-pyran-4-ones[1] during the last decade. This was motivated by three factors: (1) improved methods of preparation;[2] (2) discovery and synthesis of natural products possessing this heterocycle;[3] and (3) usefulness of dihydro-γ-pyrones as intermediates in natural product synthesis.[4] The early examples of oxidative Ferrier rearrangement[5] of glucals to unsaturated lactones were reported by Rollin[6a] and Jargils.[6b] Although the products were obtained in good isolated yields, the vigorous reaction conditions (PCC, hot $ClCH_2CH_2Cl$ or m-CPBA, $BF_3.Et_2O$) preclude the presence of reactive and sensitive functional groups in the substrates. We report herein an extremely facile, efficient and mild alkylative 1,3-carbonyl transposition[7] of dihydro-γ-pyrones (2) to unsaturated δ-lactones (4).[8]

In spite of a number of synthetic methods available for the preparation of dihydropyrones,[2] none appeared to be well-suited for 3-substituted-2,3-dihydro-4H-pyran-4-ones (2). Even the exemplary hetero Diels-Alder cycloaddition of Danishefsky[2a] cannot be easily adapted because it will necessitate synthesis of the appropriate 4-substituted Danishefsky's diene. We prepared the various α-substituted dihydropyrones from the corresponding alkylated ethyl acetoacetates. Thus, treatment of 3-alkyl-4-hydroxy-2-butanones (1)[9] with $SnCl_4$ (1.0 M in CH_2Cl_2, 2.0 eq.) and $HC(OEt)_3$ (2.0 eq.) at -40^oC-->-10^oC for 1hr

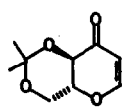
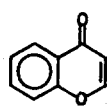
#Dedicated to Prof. M. V. George on the ocassion of his 65th birthday



1 2 3 4

a) $SnCl_4$, $HC(OEt)_3$, -40°C--->-10°C, 1hr, CH_2Cl_2; b) $(R_2)Li$, -78°C, Et_2O; c) PCC, rt, 45 min, CH_2Cl_2.

Table - Preparation of dihydropyrones and lactones

Entry	Substrate	Isolated yields of (%) 2[a]	3[b]	4[a]
a)	R_1 = Bn; R_2 = n-Bu	91	>95	72
b)	R_1 = Bn; R_2 = Me		>95	77
c)	R_1 = allyl; R_2 = n-Bu	84	>95	74
d)	R_1 = allyl; R_2 = Me		>95	69
e)	R_1 = n-Bu; R_2 = n-Bu	87	>95	77
f)	R_1 = n-Bu; R_2 = Me		>95	70
g)	 R_2 = n-Bu	--[c]	>95	79
h)	R_2 = Me		>95	74
i)	 R_2 = n-Bu	--[d]	>95	57
j)	R_2 = Me		>95	56

[a]Purified by SGC. [b]Crude. [c]Prepared from tri-O-acetyl-D-glucal *Can. J. Chem.* **1973** 51 3950. [d]Prepared from o-hydroxyacetophenone *J. Am. Chem. Soc.* **1950** 72 3396.

Experimental procedure for dihydropyrones (2): To a solution of $HC(OEt)_3$ (2.0 mmol) in 2 ml of dry CH_2Cl_2 at -40°C under N_2 was added dropwise a solution of freshly distilled $SnCl_4$ (1.0 M in CH_2Cl_2, 2.0 mmol). After 15 min. β-hydroxy ketone (1) (1.0 mmol in 1 ml CH_2Cl_2) was added. After 1hr (-40°C--->-10°C) the reaction was quenched with sat. aq. $NaHCO_3$. Work-up followed by SGC afforded dihydropyrone (2).

afforded the somewhat unstable α-alkylated dihydropyrones (2) in >80% yield after silica gel chromatography (SGC). Addition of alkyl lithium (-78 °C) provided a crude mixture of diastereomeric tertiary allylic alcohols (3) in quantitative yield; attempted SGC of the acid labile pyranols led to significant decomposition. The oxa analog of 1,3-transposition[7] of dihydropyranols (3) to unsaturated-δ-lactones (4) proceeded smoothly with PCC[10] (1.5 eq.) in CH_2Cl_2 at ambient temperature. A variety of α,β-unsaturated δ-lactones (4a-h) were synthesised from dihydro-γ-pyrones (2a-h) in 70-80% overall yield.[11,12] The conversion of benzopyranols 3i,j to coumarins 4i,j was clean and rapid using CrO_3.2Py[13] instead of PCC.

It is clear from the examples in Table that a large variety of substrates can be smoothly processed through the PCC mediated oxidative transformation. Two examples clearly underscore that the sequence is compatible with reactive and sensitive moiety in substrates. The allyl substituted pyranols (3c,d) gave the expected lactones (4c,d) as the sole product; none of the bicyclic γ-lactone arising from oxidative cleavage of the olefin[14] was observed in the crude residue. Also, the acid labile acetonide protecting group survives the conversion of glucals 2g,h to lactones 4g,h. In order to compare the relative rates of rearrangement + C-2 oxidation vs C-4 oxidation, we subjected secondary pyranol 3k (R_1=Bn, R_2=H) to rearrangement conditions. The crude residue consisted of 75:25 mixture of lactone and pyrone, respectively.

In conclusion, we have developed an efficacious protocol for dihydro-γ-pyrone annulation and their transformation to substituted δ-lactones. Its application in the asymmetric synthesis of natural products is being explored.

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11. Physical data for some representative compounds synthesised.

2a: 1H NMR (CDCl3, δ) 7.32-6.96 (m, 6H); 5.32 (d, J=8Hz, 1H); 4.20 (dd, J=12,6 Hz, 1H); 4.00 (dd, J=12,8 Hz, 1H); 3.10 (dd, J=12,10 Hz, 1H); 2.84-2.24 (m, 2H). 13C NMR (CDCl3, δ): 193.66, 162.90, 138.13, 128.89, 128.59, 126.53, 106.40, 70.29, 46.29, 32.47. IR (Neat, cm-1): 1660, 1590 (partial). Analysis: Calcd for C12H12O2 C 76.57, H 6.43; Found C 76.42, H 6.38. Mass: M+ 188.

2c: 1H NMR: 7.28 (d, J=6 Hz, 1H); 5.96-5.52 (m, 1H); 5.34 (d, J=6Hz, 1H); 5.20-4.88 (m, 2H); 4.56-3.96 (m, 2H); 2.72-1.96 (m, 3H). 13C NMR: 193.77, 162.95, 134.60, 117.66, 106.54, 70.83, 43.94, 30.15. IR: 1700, 1650, 1580. Analysis: Calcd for C8H10O2 C 69.54, H 7.30; Found C 69.50, H 7.35.

2e: 1H NMR: 7.22 (d, J=6Hz, 1H); 5.32 (d, J=6Hz, 1H); 4.52-4.00 (m, 2H); 2.52-2.16 (m, 1H); 1.48-1.00 (m, 6H); 0.86 (t, J=4Hz, 3H). 13C NMR: 194.89, 163.69, 106.42, 71.42, 44.65, 29.88, 26.24, 22.41, 13.59. IR: 1700, 1650. Analysis: Calcd for C9H14O2 C 70.10, H 9.15; Found C 70.15, H 9.09.

3a: 1H NMR: 7.40-7.08 (m, 5H); 6.42 (d, J=6Hz, 1H); 4.81 (d, J=6Hz, 1H); 4.20-3.95 (m, 1H); 3.85 (dd, J=10,5 Hz, 1H); 3.64 (t, J=6Hz, 1H); 3.00 (dd, J=14,4 Hz, 1H); 2.48-2.28 (m, 1H); 2.18-1.98 (m, 1H); 1.80-1.10 (m, 6H); 0.93 (t, J=7Hz, 3H). IR: 3400, 2900, 1640.

4a: 1H NMR: 7.40-7.04 (m, 5H); 5.80 (br s, 1H); 4.16 (m, 2H); 3.04-2.48 (m, 2H); 2.44-2.04 (m, 3H); 1.80-1.12 (m, 4H); 0.92 (t, J=6Hz, 3H). 13C NMR: 165.59, 164.65, 138.48, 129.19, 128.89, 126.95, 115.35, 68.42, 39.89, 36.00, 34.53, 28.75, 22.25, 13.76. IR: 1710. Analysis: Calcd for C16H20O2 C 78.65, H 8.25; Found 78.75, H 8.22. Mass: M+ 244.

12. All new compounds displayed IR, 1H and 13C NMR, and combustion data compatible with their structures.

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