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A Convenient Synthesis of Unsymmetrical, Substituted γ-Pyrones from Meldrum's Acid

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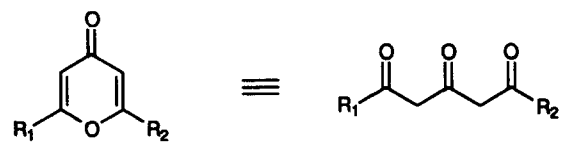
Abstract: *A unique approach to the synthesis of mono and disubstituted γ-pyrones from acylated Meldrum's acid and vinyl ethers has been developed. The convenient one pot synthesis of these versatile polyketide equivalents is accomplished without strong base or low temperatures.*

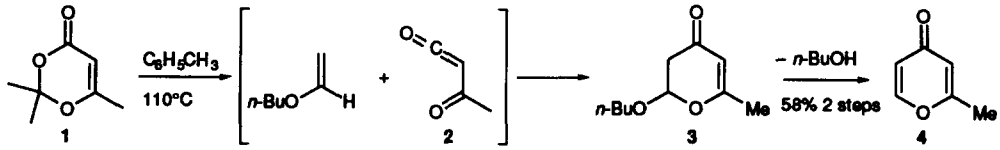
Recent studies have demonstrated that substituted γ-pyrones are versatile intermediates in organic synthesis. They can be used as polyketide synthons in the synthesis of polyacetate and spiroketal containing natural products[1] and as cycloaddition substrates for the construction of complex polycyclic systems.[2] The utilization of these important synthetic building blocks requires an efficient, general synthesis of unsymmetrical, substituted γ-pyrones. Existing methods include the acylation of 4-methoxy-3-buten-2-one[3] or methoxy-butenyne[4] followed by acid catalyzed hydrolysis and cyclization. These methods for the preparation of γ-pyrones require strong base and low temperatures and, as a result, are not readily amenable to scale-up.

γ-pyrone
4H-pyran-4-one



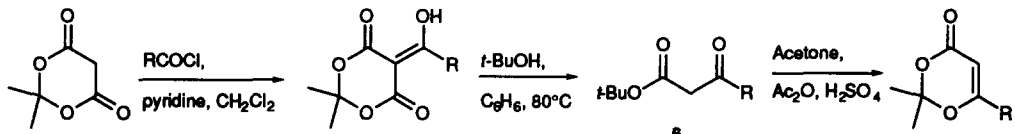
A recent report by Coleman and Grant describing the synthesis 4-pyranones by the slow addition of 2,2,6-trimethyl-1,3-dioxin-4-one **1** to a solution of n-butylvinyl ether in toluene at reflux noted the isolation of 2-methyl-γ-pyrone **4** as a side product in the reaction.[5] The dioxinone **1** extrudes acetone to generate an acyl ketene **2** which undergoes a [4+2] cycloaddition with the enol ether. The 2-methyl pyrone **4** apparently arises from simple elimination of n-butanol. We felt that it should be possible to manipulate this reaction and effect exclusive formation of the γ-pyrone. Reaction of *n*-butyl vinyl ether with dioxinone **1** as reported by Coleman gave the 2-(1-butoxy)-6-methyl-2,3-dihydro-4H-pyran-4-one **3**. Initial attempts at eliminating the n-butanol using a variety of acidic and basic conditions gave disappointing results, but ultimately the pyrone was obtained by simply heating the crude, neat pyranone **3** to ~170 °C. The addition of a high boiling solvent (i.e. p-cymene) improved the yield by reducing the decomposition observed with the neat pyranone. The 2-methyl-γ-pyrone was obtained by this sequence in 58% overall yield without the need for strong bases or low temperatures (Scheme 1).

Scheme 1



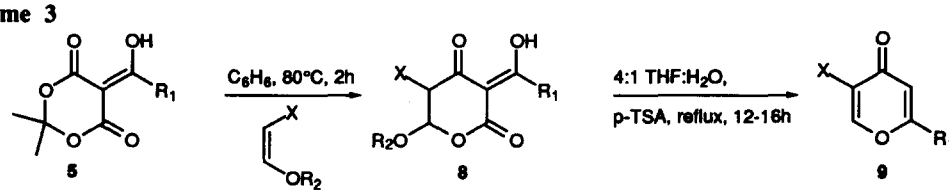
This synthesis represents a new approach to mono substituted γ-pyrones and we were interested in extending this methodology to the preparation of other substituted pyrones. 2,2,6-Trimethyl-1,3-dioxin-4-one **1**, the acetone adduct of diketene, is commercially available but other analogs would need to be synthesized. These dioxinone derivatives **7**[7] can be prepared from malonic acid as shown in Scheme 2. Malonic acid is treated with acetone, acetic anhydride and catalytic H_2SO_4 to generate the acetone adduct which is commonly referred to as Meldrum's acid.[6] Meldrum's acid was readily acylated[8] with an acid chloride and pyridine to give **5**. Diester **5** was converted to a t-butyl ester **6** upon treatment with t-butanol in benzene[9] at reflux and the acid labile ester was cyclized to the dioxinone **7** using conditions similar to those used for the preparation of Meldrum's acid. A series of analogs were prepared in this manner (Scheme 2).

Scheme 2



Conversion of the acylated Meldrum's acid **5** to the t-butyl ester **6** involves the addition of *t*-butanol with subsequent loss of acetone and carbon dioxide which helps drive the reaction. This particular cascade of events prompted us to investigate whether it might be possible to effect the loss of acetone and carbon dioxide under thermal conditions to generate an acyl ketene. The pyranone could then be obtained as reported above. The initial attempts at mimicking the conditions used earlier with dioxinone **1** (slow addition of acylated Meldrum's acid **5** to a solution of n-butyl vinyl ether in toluene at reflux) gave predominately the n-butyl *beta*-keto ester. Repeated modifications eventually led to the formation of a pyrandione **8** rather than the expected pyranone (Scheme 3). The unexpected product is believed to arise not from the acyl ketene but rather from a sequence in which the vinyl ether adds to the acylated Meldrum's acid with assistance from the oxygen to give an oxonium species. Acetone is then lost, but before decarboxylation can occur the intermediate closes to the pyrandione. While this product was unexpected, it can be readily transformed to the γ-pyrone by treatment with p-TSA in a 4:1 THF:H_2O mixture at reflux. A variety of acid chlorides and vinyl ethers have been used to construct mono-,

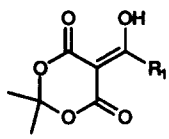
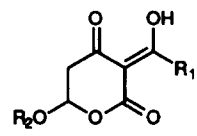
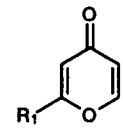
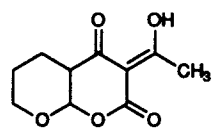
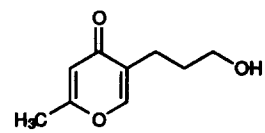
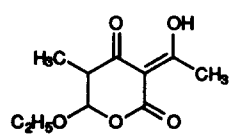
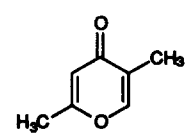
Scheme 3



di- and trisubstituted pyrones (Table1). The substituted γ-pyrones were isolated in modest to very good yields. The Meldrum's acid approach has advantages over other methods[3,4] because the starting materials are inexpensive and the procedure does not require strong bases or low temperatures. Also, slow addition (via a syringe pump) of the acylated Meldrum's acid is not necessary as in the acyl ketene approach. The acylated Meldrum's acid is simply dissolved in benzene with five equivalents of vinyl ether and warmed to reflux. Benzene is typically used (the optimal temperature seem to be around 80 °C) but THF has also been used successfully.

A general procedure is as follows: In a flame dried round bottom flask fitted with a condenser, were dissolved acylated Meldrum's acid (2.7 mmol) and dry n-butyl vinyl ether[10] (13 mmol) in dry benzene (0.5 M with respect to the Meldrum's acid). The solution was warmed to reflux and followed by TLC until the acylated Meldrum's acid was consumed (2h). The volatile components were then removed under reduced pressure and the residue was taken up in a 4 to 1 THF/H_2O mixture (0.15 M with respect to acylated Meldrum's acid). p-TSA (10 mol%) was added and the solution warmed to reflux for 16-20 h. The volume was reduced to 1/3 and the residue taken up in CH_2Cl_2. The mixture was extracted with distilled H_2O and saturated aqueous NaCl, and then the combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude γ-pyrone can be purified by flash chromatography or vacuum distillation. Structure identification was determined by IR, ^1H and ^{13}C NMR.

Table

Acylated Meldrum's Acid	Pyranone	Pyrone	(Yield)
			
R_1 = CH_3	R_2 = n-C_4H_9	R_1 = CH_3	(73)
R_1 = CH_3	R_2 = t-C_4H_9	R_1 = CH_3	(61)
R_1 = C_2H_5	R_2 = n-C_4H_9	R_1 = C_2H_5	(75)
R_1 = $(CH_3)_2CH$	R_2 = n-C_4H_9	R_1 = $(CH_3)_2CH$	(57)
R_1 = $C_6H_5CH_2$	R_2 = n-C_4H_9	R_1 = $C_6H_5CH_2$	(85)
R_1 = CH_3			(53)
R_1 = CH_3			(40)

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9. All new compounds gave consistent ^{1}H ^{13}C and IR spectra as well as satisfactory C, H combustion analyses or HRMS. All yields are for homogeneous, chromatographically pure products unless otherwise indicated.

10. Distillation of the *n*-butyl vinyl ether from sodium metal or calcium hydride prior to use is recommended.

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