

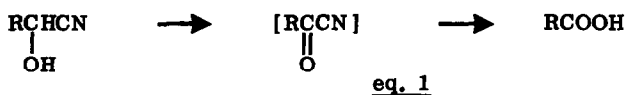
A SIMPLE ROUTE TO Δ^2 -BUTENOLIDES FROM CONJUGATED ALDEHYDES

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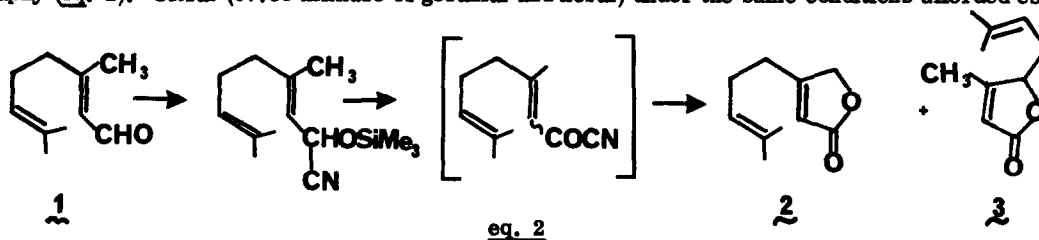
Summary: A variety of Δ^2 -butenolides may be synthesized by oxidation of the O-trimethylsilylcyanohydrins of α,β -unsaturated aldehydes using pyridinium dichromate in dimethylformamide.

Pyridinium dichromate (PDC) is an especially useful oxidant for organic synthesis in aprotic media.^{1,2} In dimethylformamide (DMF) solution at 0° allylic alcohols are oxidized to α,β -unsaturated aldehydes but not further, although non-conjugated aldehydes are oxidized to carboxylic acids under the same conditions (the latter process is especially fast and efficient at 25°). In view of these results it became of interest to investigate the oxidation of cyanohydrins derived from conjugated and non-conjugated aldehydes using PDC in DMF. It was discovered that whereas the cyanohydrins of non-conjugated aldehydes are oxidized to carboxylic acids using PDC in DMF in excellent yields (eq. 1), the cyanohydrins of conjugated aldehydes (as the O-trimethyl-



silyl derivatives) behaved completely differently, yielding α,β -unsaturated γ -lactones (Δ^2 -butenolides) as major products in those cases in which (a) the β -carbon was disubstituted and (b) the γ -carbon possessed at least one hydrogen.

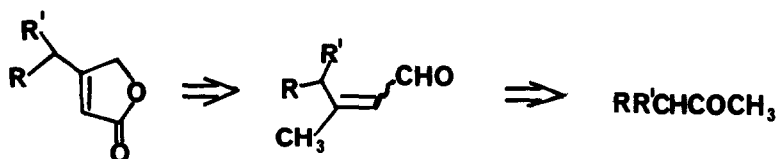
The oxidation of geranial (**1**) is fairly typical. After formation of the O-trimethylsilylcyanohydrin of geranial by treatment with 1.1 equiv. of trimethylsilylcyanide (TMSCN) in methylene chloride at 0° for 15 min. in the presence of a catalytic amount of potassium cyanide/18-crown-6 complex,³ concentration under reduced pressure and treatment with 3 mole equiv of PDC in DMF (12 hr. at 25°), there was obtained a mixture of the two isomeric Δ^2 -butenolides **2** and **3** (ratio 4:1) in 73% yield (eq. 2) after extractive workup and chromatography (eq. 2). Citral (67:33 mixture of geranial and neral) under the same conditions afforded essentially



the same mixture of **2** and **3**.

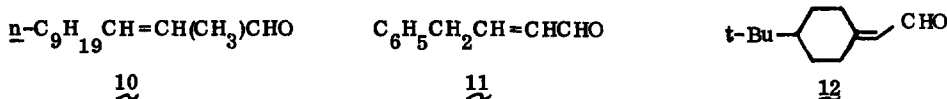
Seven other examples of this oxidative lactonization are presented in Table I. In some cases (e.g. 4,5) only a single Δ^2 -butenolide unit is produced. The tendency for oxygenation at γ -methyl vs γ -methylene is also apparent. Since the Δ^2 -butenolide unit is found in a large number of naturally occurring

substances having a wide variety of physiological properties,^{5,6} and since there are several practical routes to the requisite α, β -unsaturated aldehydes,⁷ the synthesis of Δ^2 -butenolides reported here may be advantageous in certain instances. In the synthetic sense a target Δ^2 -butenolide may be disconnected to simpler precursors as shown in eq. 3.

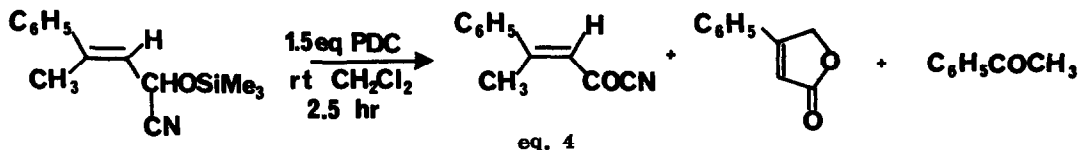


eq. 3

The scope of the oxidative conversion of O-trimethylsilyl-cyanohydrins of α, β -unsaturated aldehydes to Δ^2 -butenolides is subject to limitations. Under the conditions outlined above for Δ^2 -butenolide formation, no Δ^2 -butenolide could be detected from the O-trimethylsilyl-cyanohydrins of the aldehydes 10, 11 and 12.

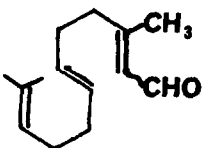
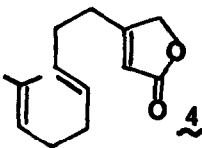
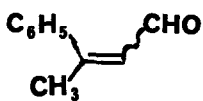
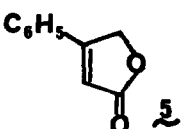
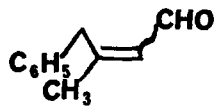
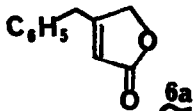
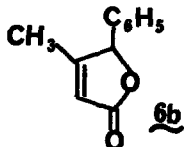
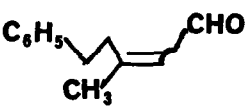
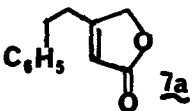
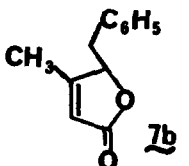
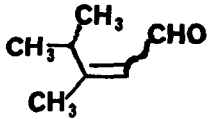
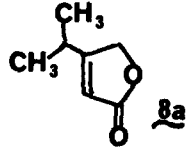
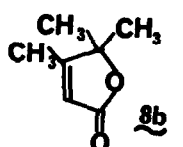

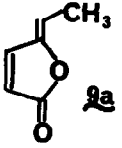
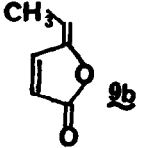
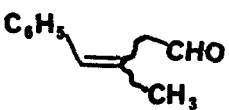
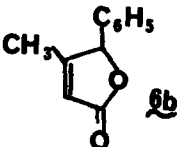


With regard to mechanism, it seems reasonable that the initial stage could be desilylation and oxidation of the chromate ester of the cyanohydrin to an acyl cyanide. Experimental evidence suggests that this is indeed the case. Treatment of the O-trimethylsilyl cyanohydrin of geranial with 1.5 equiv. of PDC in methylene chloride at 23° results in formation of detectible amounts of cyanohydrin as well as two new products which are gradually converted to a mixture of the Δ^2 -butenolides 2 and 3. If the reaction is interrupted after 5 hr., a mixture of isomeric E and Z acyl cyanides can be isolated in 58% yield together with 25% of a mixture of the isomeric Δ^2 -butenolides 2 and 3 (eq. 2). The acyl cyanides⁸ are obtained in pure form by rapid chromatography on silica gel. Upon treatment with 3 equiv. of PDC in DMF at 23° for 30 min. they are oxidized smoothly into a mixture of Δ^2 -butenolides 2 and 3 (ratio 3:1) in 91% yield. The E/Z acyl cyanides are converted to 2 and 3 in methylene chloride at 23° using 3 equiv. of PDC but the reaction is considerably slower than in DMF and requires ca. 36 hr. (82% yield of 2 and 3 in a ratio of 58:42). Other conjugated acyl cyanides can be prepared similarly using methylene chloride as solvent and 1.5 equiv. of PDC at 23°, however the oxidation is not generally efficient since Δ^2 -butenolide and other by-products are usually formed in addition to acyl cyanide, as indicated by the example in eq. 4.



eq. 4

Table I. Conversion of α,β -Unsaturated Aldehydes to Δ^2 -Butenolides^a

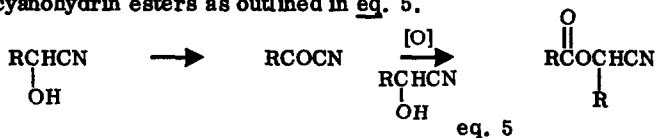
Aldehyde	Ratio ^b (E:Z)	Products ^c	Ratio ^b (a:b)	Isolated Yield, %
	68:22		c	69
	59:41		-	71
	63:37	 	36:64	54
	63:37	 	77:23	68
	79:21	 	>95:5	75
	--	 	54:46	50
	--		c	40

(a) All reactions were performed following the standard procedure described in the text.

(b) Determined by integration of the appropriate resonances in the pmr spectra.

(c) Isomeric Δ^2 -butenolide not detectable by pmr analysis.

Unconjugated cyanohydrins themselves are not satisfactory substrates for the synthesis of acyl cyanide using PDC in methylene chloride, since they seem to add to the initially formed acyl cyanides leading ultimately to cyanohydrin esters as outlined in eq. 5.⁹



References and Notes

1. E. J. Corey and G. Schmidt, Tetrahedron Letters, 399 (1979).
2. W. M. Coates and J. R. Corrigan, Chem. and Ind., 1594 (1969).
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 (b) A. Hertenstein, S. Hunig and M. Oller, Synthesis, 416 (1976);
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5. For reviews see: (a) Y. S. Rao, Chem. Rev., 76, 625 (1976); (b) A. A. Avetisyan and M. T. Dangyan, Russ. Chem. Rev., 46, 643 (1977); (c) R. C. Larock, B. Riefling and C. A. Fellows, J. Org. Chem., 43, 131 (1978).
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 (b) J. E. McMurry and S. F. Donovan, Tetrahedron Lett., 2869 (1977); A. Cowell and J. K. Stille, ibid., 133 (1979); D. Caine and A. S. Frobese, ibid., 5167 (1978) and references cited.
7. For an excellent review of recent methods see: S. F. Martin, Synthesis 633 (1979).
8. Pmr in CDCl_3 (δ , partial) 6.20 (1q, 1H, $\text{C}=\text{C}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}\text{CN}$); 5.04 (1H, m, $(\text{CH}_3)_2\text{C}=\text{CH}-$), 2.28 (E) and 2.05 (Z) (d, $J=1.2$ Hz, 3H, $\delta\text{-CH}_3$); 1.70 and 1.62 (6H, s, CH_3). (Ir film, partial) cm^{-1} 2232 (CN), 1670, 1642, 1601, 1442, 1378, 1242, 1210 and 1107.
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