IODOVINYLIDENE LACTONE SYNTHESIS. FREE RADICAL CYCLISATION OF IODO ACETYLENIC ESTERS.

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Abstract: Propiolic acids add to alkenes in the presence of N-iodosuccinimide to give iodo acetylenic esters. These, on treatment with dibenzoyl peroxide, undergo cyclisation to yield (E)-iodovinylidene butyrolactones. Subsequent alkylation with lithium dimethylcuprate occurs by replacement of the iodine.

In view of the intense interest in α -methylene- γ -butyrolactones¹, coupled with the many reports of syntheses of five membered rings by exo-trig additions of free-radicals to multiple bonds², it is somewhat surprising that methodologies involving the exo-dig addition of a free-radical to a triple bond have not featured prominantly among the reported routes to this class of compounds. In fact, in a recent review of the synthesis of α -methylene- γ -butyrolactones¹, exo-dig formation of the β,γ -bond was not cited as a key synthetic bond connection. A more general review of α -methylene lactone synthesis³ also showed that this route had been little exploited. To date, the only reported syntheses of this type have involved the addition of propargyl alcohol to a double bond, followed by radical induced cyclisation and oxidation of the ensuing methylene tetrahydrofuran⁴.

Our aim was to add α -alkylidene lactone units to an existing double bond in a more direct fashion. The requisite functionality was readily provided by treatment of the alkene (1) with the desired carboxylic acid in the presence of a source of iodonium ion.



Two suitable reagents proved to be I(py), BF. 3 and N-iodosuccinimide 6. Of these two, the

latter provided more reproducible yields and adapted well to larger scale synthesis. Results of additions performed with N-iodosuccinimide are summarized in the Table.





Table. Iodoester preparations and cyclisations.

Ester	Preparation [*]				Cyclisation		
	Time/h	Temperature/°C	Yield [*] /%	Method	Time/h	Yield [°] /%	
2a (n=3)	0.3	0	80	h v ⁴	0.1	21 (4% (<i>Z</i>))	
				DBP*	3.0	47	
2b (n=3)	2.5	20	78	hν	0.1	24 (28% (<i>Z</i>))	
				DBP	2.3	88	
2c (n=3)	2.0	0	64	DBP	1.0	85	
2a (n=4)	0.3	20	39	hν	0.1	23 (6% (Z))	
				DBP	24.0	37	
2b (n=4)	2.5	20	85	hv	0.4	47 (11% (<i>2</i>))	
				DBP	7.5	59	
2c (n=4)	2.0	20	82	DBP	1.7	93	
3	4.0	20	98	DBP	14.0	63	
4	0.3	~5	60	DBP	2.0	75	

*Alkene (1.0 mmole), carboxylic acid (2.0 mmole) and N-iodosuccinimide (1.3 mmole) in CHCl₂ (15 cm³).

'Isolated by centrifugal chromatography on silica (ether/hexane 3:7)'. Based on alkane.

[°]Isolated yield of (E)-iodovinylidene lactone (purified by radial chromatography on silica). New compounds gave satisfactory microanalytical data.

⁴A stirred solution of the iodoester (1.6 mmole) in acetonitrile (7 cm³) was irradiated, under an atmosphere of N_2 , in the presence of zinc dust (3.0 mmole), at 253 nm in a Rayonet Photochemical Reactor.

*Iodoester (1.0 mmole) and dibenzoyl peroxide (0.1 mmole) heated under reflux in benzene (2 cm³).

Various methods to induce cyclisation by formation of a free-radical by C-I bond cleavage were investigated. Photolysis at 235 nm in the presence of zinc dust gave low to moderate yields of mixtures of unsaturated lactones. With propiolate esters (2a), the (E) and (Z)-iodomethylene lactones (6a) and (7a) were formed^{*}, along with small quantities of the methylene lactone (5a).



Several reports of production of iodo compounds from cyclisation of iodo alkenes or iodo acetylenes have appeared recently, and an atom transfer mechanism has been proposed⁵. Such a mechanism appeared to operate here, as the proportions of the iodo compounds (6a) and (7a) could be enhanced by using higher substrate concentrations. As solvents such as tert-butyl alcohol and acetonitrile were most effective, a polar transition state, such as has been proposed in other free-radical halogen abstraction processes^{1.9}, would appear to be implicated. Photolysis in the absence of zinc dust was unsuccessful.

A substantial improvement in the cyclisation step was achieved by heating the iodoesters with dibenzoyl peroxide. Unlike the photolytic process, this reaction gave only iodinated lactones and these were formed solely as the (E)-geometric isomer (6). With both cyclopentyl and cyclohexyl systems (n = 3 and 4 respectively), reaction with the propiolic esters (2a) proceeded sluggishly and in moderate yield. However, in the case of the tetrolic (2b) and trimethylsilylpropiolic (2c) esters, the reaction proceeded readily and in high yield (Table). The acyclic alkenes, styrene and 2,3-dimethyl-2-butene, were also transformed in good yield into iodoethylidene lactones (8) and (9) respectively.



This method provides ready access to a variety of α -iodovinylidene- γ -butyrolactones. The reaction is stereospecific and the presence of the iodo function provides for further modification of the carbon skeleton. To demonstrate this, we reacted the iodoethylidene lactone (6b) with lithium dimethylcuprate and obtained the isopropylidene lactone (10b).



Methylation of the (E)-iodomethylidene lactone (6a) proceeded with retention of stereochemistry to give ethylidine lactone (10a). The (Z)-iodoethylidene lactone isomer (7b), which had been obtained from the photolytic cyclisation of (2b), was also methylated but gave both geometric isomers.

The species (6c) which contain both iodo and trimethylsilyl groupings on the β -carbon have an interesting juxtaposition of functionality which provides scope for a wide range of chemistry which we have yet to explore.

References and Notes

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- 8. The (E) and (Z)-isomers were distinguishable by their ¹H n.m.r. spectra. The (E)-iodomethylene lactone (6a, n=4) showed a one proton signal at δ 7.59 while the corrresponding signal for its (Z)-isomer (7a, n=4) was at δ 7.12. The ethylidene lactones showed a corresponding variation in the methyl proton resonance frequencies ((E)-isomer (6b, n=4) δ 3.05; (Z)-isomer (7b, n=4) δ 2.75). The cis ring geometries were shown by the narrow $W_{h/2}$ of the ring junction proton signals (typically ca 15 Hz).
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