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TOSYLOXYLACTONIZATION OF ALKENOIC ACIDS WITH [HYDROXY(TOSYLOXY)IODO]BENZENE

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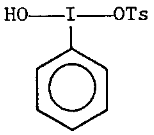
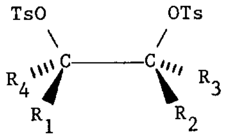
Summary: [Hydroxy(tosyloxy)iodo]benzene(1) reacts with 3-butenoic, 4-pentenoic, 5-hexenoic and 2-methyl-4-pentenoic acids in CH_2Cl_2 to give tosyloxylactones and with *trans*-3-hexenoic and 2-cyclopenteneacetic acids to give unsaturated lactones. 5-Norbornene-*endo*-2-carboxylic acid with 1 gives a rearranged lactone while 5-norbornene-*endo*-2,3-dicarboxylic acid gives a *bis*-lactone.

The general utility of the iodo-[1,2] and phenylselenolactonization[3] reactions in organic synthesis prompted us to investigate the reactions of [hydroxy(tosyloxy)iodo]benzene(1)[4-6] with a series of representative alkenoic acids. A previous finding that 1 reacts with various alkenes to give *vic*- bis(tosyloxy)alkanes(2) with *cis* stereospecificity[7,8] suggested that alkenoic acids might give tosyloxylactones with 1.



1

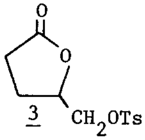
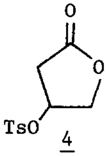
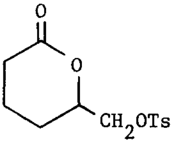
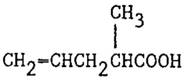
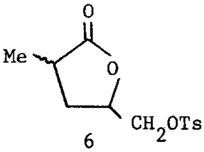
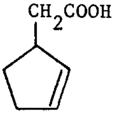
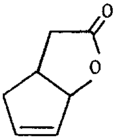
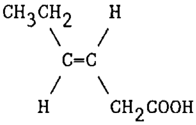
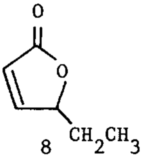


2

When a solution of 4-pentenoic acid (11 mMol) in CH_2Cl_2 (5 mL) was added dropwise at room temperature to a stirred mixture of 1 (10 mMol) and CH_2Cl_2 (60 mL), heat was evolved, and most of the hypervalent iodine reagent disappeared within 15 minutes. After six hours, the reaction mixture was washed (water, satd $NaHCO_3$, brine), dried and concentrated to an oil. Treatment of the oil with ether (removes iodobenzene) delivered 5-tosyloxy-4-pentanolactone(3) in 60 % yield: mp 80.5-81.5°C; IR(film) 1784 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.7-2.7 and 2.42(complex m and s, 7H), 4.1(unsym. three-line m, 2H), 4.59("septet", 1H), 7.46(AA'BB' m, 4H); Anal. C, 53.04%; H, 5.19%.

Similar treatment of 3-butenoic, 5-hexenoic and 2-methyl-4-pentenoic acids with 1 in

Table I. Reactions of Alkenoic Acids with [Hydroxy(toxyloxy)iodo]benzene.

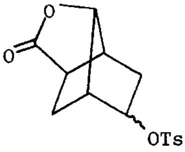
Alkenoic Acid	Reaction Conditions	Product[c]	Yield[d], Mp[e]
$CH_2{=}CH(CH_2)_2COOH$	CH_2Cl_2, 6h, r.t.[a]	 3	60%, 80.5-81.5°C
$CH_2{=}CHCH_2COOH$	CH_2Cl_2, 3h, reflux[b]	 4	55%, 109-112°C
$CH_2{=}CH(CH_2)_3COOH$	CH_2Cl_2, 3.5h, r.t.[a]	 5	52%, 78-79°C
 $CH_2{=}CHCH_2CH(CH_3)COOH$	CH_2Cl_2, ~ 2h, r.t.[a]	 6	65%, 92-95°C
	CH_2Cl_2, 4h, r.t.[a] DBU	 7	56%, oil
 $CH_3CH_2CH{=}CHCH_2COOH$	CH_2Cl_2, 5h, r.t.[a] DBU	 8	32%, oil

[a] 10.0 mMol each of acid and 1. [b] 23 mMol each of acid and 1. [c] Compounds 3, 4, 5, 6, and 8 were characterized by spectral (IR, ^1H NMR) and elemental analysis; the C,H percentages were within +0.4% of the calculated values in all cases. Compound 7 was identified by comparison of its spectra (IR, ^1H NMR) with those of the authentic material prepared by the phenylselenolactonization method. [d] Yields are based on crude products, most of which were reasonably clean (by NMR). Crude 7 contained an obvious impurity (AA'BB' m in the ^1H NMR spectrum). [e] Uncorrected.

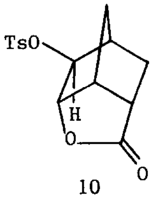
CH_2Cl_2 gave moderate yields of 3-tosyloxy-4-butanolactone(4), 6-tosyloxy-5-hexanolactone(5) and 5-tosyloxy-2-methyl-4-pentanolactone(6), all as crystalline solids; see Table I. The reactions of alkenoic acids with 1 typically proceed with the formation of some p-toluenesulfonic acid. For example, in one experiment with 3-butenoic acid, the yield of p-TsOH, determined by titration of the aqueous extract from the initial workup, was found to be 39%.

In some cases, tosyloxylactones were not isolated. Thus, 2-cyclopenteneacetic and trans-3-hexenoic acids reacted with 1 to give the unsaturated lactones 7 and 8 and high yields (70% and 71%) of p-TsOH.[9] Although tosyloxylactones may also have been present in the crude product mixtures, they were not successfully separated, and the yields of 7 and 8 given in Table I are based upon treatment of the product mixtures with DBU prior to chromatographic isolation.

5-Norbornene-endo-2-carboxylic acid reacted with 1 in CH_2Cl_2 to give a low yield of a tosyloxylactone tentatively assigned the rearranged structure 9[10] (21% yield at room temperature, 28% yield at ca. 0°C.) and a high yield (57%, 60%) of p-TsOH. That the structure of the product is neither 10 nor 11 was confirmed by comparison of its melting point and spectra (IR, ^1H NMR) with those of the known compounds.[11]



9



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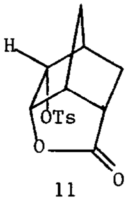

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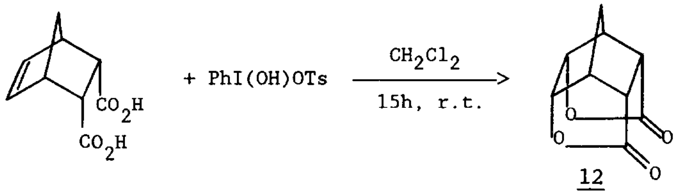
When 5-norbornene-endo-2,3-dicarboxylic acid was mixed with 1 in CH_2Cl_2, the products were p-toluenesulfonic acid and the bis-lactone 12 (mp 273-275°C [lit.[12] mp 263°C]); eq 1. After the p-TsOH was removed, the filtrate was washed (water, satd $NaHCO_3$, brine), dried and concentrated. Treatment of the residual material with ether gave 12 in 49% yield. The monomethyl ester of the diacid reacted similarly with 1.



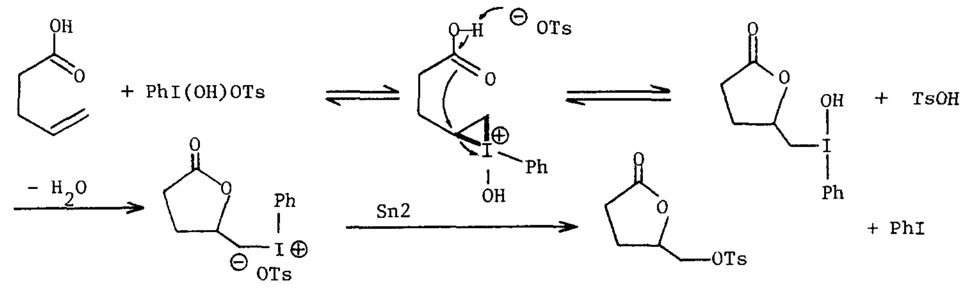
12

+ p-TsOH (1)
(89%)*

* based on assumption that isolated material was the monohydrate

A plausible mechanism for the tosyloxylactonization of alkenoic acids with 1 is illustrated in Scheme I with 4-pentenoic acid.

Scheme I



A key feature of this mechanism is the proposal of two nucleophilic displacements at carbon, both with inversion of configuration, and the expectation, therefore, of a cis-relationship between the lactone ring and the tosyloxy function. Unfortunately, 2-cyclopenteneacetic acid and 5-norbornene-endo-2-carboxylic acid, both likely substrates for the elucidation of the stereochemistry of tosyloxylactonization, exhibited divergent modes of reactivity, and the sterochemical question needs yet to be resolved.

References and Notes

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9. The yields of p-TsOH were determined by titration of the aqueous extracts of initial reaction mixtures in separate experiments from those for which the lactone yields in Table I are given.

10. The same product, obtained from reaction of an endo:exo mixture of 5-norbornene-2 carboxylic acid with 1, was characterized by elemental (C,H) and spectral (IR, ^{1}H NMR) analysis. The product obtained from the endo acid was identified by comparison of its melting point and spectra with those of the former.

11. We wish to thank Dr. Robert M. Moriarty (University of Illinois, Chicago campus) for providing us with melting points and spectra of compounds 10 and 11, previously prepared in his laboratory.

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