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Research Article

ONE POT SYNTHESIS OF IODOHYDRINS FROM STEROIDAL ALKENES

M. Mushfiq*, Sultanat and Rakhshanda Rehman

Department of Chemistry, Aligarh Muslim University Aligarh, India.

***Corresponding Author: chemistry.organic@rediffmail.com**

ABSTRACT

The reaction of steroidal alkenes with iodine in aqueous 1,4-dioxane and diverse metal salts at room temperature produced the corresponding iodohydrins with $Cu(OAc)_2$ giving the highest yields. The structure of the products were confirmed by elemental analysis and spectral data (IR, ^1H NMR and ^{13}CNMR).The method is economical, environmentally friendly, convenient, one pot transformation of alkenes to corresponding iodohydrin.

Keywords: Iodohydrins, steroidal alkenes, metal salts, 1,4-dioxane,$Cu(OAc)_2$ and iodine.

INTRODUCTION

Halohydrins are valuable intermediates that can be transformed into epoxides[1], ketones[2] and other derivatives[3-5]. Chlorohydrins and bromohydrins can be prepared in good yields when the halogenation of the alkene is carried out in aqueous media[6].However the direct synthesis of iodohydrins from olefins is usually difficult to achieve.They are frequently prepared from α-iodoketones[7],epoxides[8] and other halohydrins[9] but seldom directly from alkenes because of the reversibility of steps(a) and (b) and /or the decreasing iodide concentration[6,10]as shown in Scheme 1.The reaction of alkenes with I_2-H_2O is only effective in the presence of iodide ion scavengers ($CuO.HBF_4$[11],oxidizing agents[6,10]). Although it is known that vicinal iodo-functionalization of olefins is promoted by some metal salts[11, 12]. C. A. Horiuchi [13] reported the synthesis of iodohydrins from various cycloalkenes using diverse metal salts. To the best our knowledge there is no systematic work in the literature for the preparation of iodohydrins from steroidal alkene using this methology and we now proceed in this direction.

We have made an attempt to synthesize iodohydrins from some easily accessible steroidal olefins such as 3β-acetoxycholest-5-ene (1) and 3β-acetoxystigmast-5-ene (2) using aqueous 1,4-dioxane and diverse metal salts.

EXPERIMENTAL

Melting points were recorded on a Kofler hot block apparatus and are uncorrected. IR spectra were determined in KBr with Perkins Elmer 237 spectrophotometer, ^1H NMR spectrum were run in $CDCl_3$ on Bruker AV 400 instrument with TMS as internal standard and its values are given in ppm(□□□^{13}C NMR were also run in $CDCl_3$ on Bruker DRX 300 and its values are given in ppm(□□□ TLC plates were coated with silica gel and spots were developed in iodine chamber.

General procedure

To a stirred solution of steroidal substrate (1) & (2) add $Cu(OAc)_2$[8 gm; 40 mmol] in

1,4-dioxane[20 ml] and water[20 ml], I_2 [8 gm; 31.5 mmol] in small portions at room temperature. After completion of reaction, insoluble Cu_2I_2 was filtered off, $CHCl_3$ (20 ml) was added and the organic layer was washed with a saturated solution of $Na_2S_2O_3$ (3×5 ml) and brine (5 ml). After drying over anhydrous sodium sulphate, the organic solvent was evaporated under reduced pressure. The crude product obtained was chromatographed over silica gel. Each fraction of 25 ml was taken which furnished pure compound (3a) or (4a) respectively along with its isomers as shown in Scheme 2.

3β-acetoxy-5-hydroxy-6α-iodo-5α-cholestane(3a): Elution with petroleum ether (60-80°C)/ether (95:5) gave the unreacted 3β-acetoxycholest-5-ene (1)(0.02 gm). Further elution with petroleum ether/ether (90:10) gave a solid which was recrystallized from methanol to give the compound with m.p. = 202-204°C (positive Beilstein test). IR spectrum of the compound exhibited absorption bands at 1709 (CH_3COO), 3412 (C-OH), 1048 (C-O) and 520 cm^{-1} (C-I). This shows that iodohydrin is formed and the acetoxy group is intact. ^1H NMR spectrum displayed a multiplet centered at δ 5.2 for one proton can be ascribed to C3-αH (W ½ = 15 Hz). A doublet of a doublet centered at δ 2.16 for one proton can be ascribed to C6-βH (W ½ = 13 Hz) which suggested the ring junction A/B is trans and carbon having iodine in the compound is 6-iodo. The W ½ for C6-H clearly shows that it is axial, β-oriented thus rendering the iodine as α-equatorially oriented. This discarded the structure (3c). Since A/B ring junction is trans so the structure (3b) and (3d) could be discarded wherein A/B ring junction is cis and C3-αH (equatorial) would have given a peak with J value less than 10 cps.A sharp singlet for the methyl protons of acetoxy moiety was appeared at δ 2.02 and singlet for hydroxy proton appeared at δ 3.54. Thus, the structure (3a) is preferred over the other possible structures (3b), (3c) and (3d).^{13}C NMR spectrum showed peaks at δ 76.69 for C5, δ 32.12 for C6, δ71.30 for C3 carbons and δ 170.96 for (COO). On the basis of foregoing discussion the compound may be regarded as 3β-acetoxy-5-hydroxy-6α-iodo-5α-cholestane(3a).Yield = 0.91gm.Anal.Calcd. for $C_{29}H_{49}O_3I$: C,60.83%; H,8.56%; O,8.39%; I,22.20%. Found:C,60.82%; H,8.55%; O,8.38%; I,22.19%. Molecular weight = 572, IR(KBr)ν_{max} cm^{-1}:1709cm^{-1}(CH_3COO), 3412cm^{-1}(C-OH),1048cm^{-1}(C-O) and 520 cm^{-1}(C-I),^{1}HNMR δ (ppm)$CDCl_3$= 5.2 (m, 1H, C3-αH, W ½ = 15 Hz, axial), 2.16 (dd, 1H, C6-βH, W ½ =13 Hz, axial), 2.02 (s, 3H, CH_3COO), 3.54 (s, proton of hydroxy group), 1.2 (C10-CH_3), 0.69 (C13-CH_3), 0.97 and 0.81 (other methyl protons), ^{13}C NMR δ (ppm) $CDCl_3$=C1(26.67), C2(27.98), C3(71.30), C4(36.91), C5(76.69), C6(32.12), C7(34.57), C8(35.82), C9(45.37), C10(42.73), C11(21.44), C12(39.48), C13(39.90), C14(55.82), C15(23.92), C16(28.69), C17(56.29), C18(16.68), C19(12.13), C20(29.19), C21(18.65), C22(36.16), C23(24.13), C24(38.28), C25(28.21), C26(22.79), C27(22.54), C1'(170.96), C2'(21.07).

3β-acetoxy-5-hydroxy-6β-iodo-5α-stigmastane (4a): Elution with petroleum ether (60-80°C)/ether (95:5) gave the unreacted 3β-acetoxystigmast-5-ene(2) (0.02 gm). Further elution with petroleum ether/ether (90:10) gave a solid which was recrystallized from methanol to give a compound (m.p. = 135°) (positive Beilstein test) indicating the incorporation of (OH+I) during the course of reaction, suggesting that iodohydrin is formed. The IR spectrum exhibited band at 1732 (CH_3COO), 3442 (C-OH), 1035 (CO) and 530 cm^{-1} (C-I). Therefore, the molecular composition and IR spectral values suggested the presence of iodohydrin and the acetoxy group is intact in the compound and hence four isomeric structures (4a), (4b), (4c) and (4d) could be formulated.

A clear distinction between these four isomers is possible with the help of its NMR spectrum. The ^1H NMR spectrum of the compound displayed a multiplet centered at δ4.95 for one proton (W ½ = 14 Hz) can be ascribed to C3-αH which suggested that ring junction A/B is trans. Since A/B ring junction is trans so the structure (4b) and (4d) could be discarded

wherein A/B ring junction is cis and C3-αH (equatorial) would have given a peak with J value less than 10 cps. A triplet for one proton at δ 2.19 can be taken as on carbon having iodine, this suggested that the compound is 6-iodo. The W ½ = 5.4 Hz for C6-H clearly shows that it is equatorial, α-oriented, thus rendering the iodine as β-axially oriented. This discarded the structure (4c). Other NMR values can be easily explained on the basis of structure (4a) as given. A sharp singlet for three proton appeared at δ 2.0 for methyl protons of acetoxy group. A peak at δ 3.1 can be ascribed for hydroxy proton. ^{13}C NMR shows peak at δ 71.40 for C5, δ 33.66 for C6, and δ 170.20 for (COO) carbons. Therefore, on the basis of these evidences the compound can best be characterized as 3β-acetoxy-5-hydroxy-6β-iodo-5α-stigmastane (4a). Yield = 0.90gm. Anal.Calcd. for $C_{31}H_{53}O_3I$: C,62.00%; H,8.83%; O,8.00%; I,21.16%. Found: C,61.99%; H,8.82%; O,7.99%; I,21.15%. Molecular weight=600, IR(KBr)ν_{max} cm^{-1}: 1732 cm^{-1} (CH_3COO), 3442 cm^{-1}(C-OH), 1035 cm^{-1} (C-O) and 530 cm^{-1} (C-I), ^1H NMR δ (ppm)$CDCl_3$= 4.95 (m, 1H, C3-αH, W ½ = 14 Hz, axial), 2.19 (t, 1H, C6-αH, W ½= 5.4 Hz, equatorial), 2.0 (s, 3H, CH_3COO), 3.1 (s, proton of hydroxy group), 1.15 (C10-CH_3), 0.65 (C13-CH_3), 0.95 and 0.82 (other methyl protons), ^{13}C NMR δ (ppm)$CDCl_3$=C1(27.22),C2(28.08),C3(65.16),C4(38.82),C5(71.40),C6(33.66), C7(34.99), C8(35.87),C9(45.83), C10(42.32), C11(1.33), C12(39.77), C13(42.44), C14(56.17), C15(24.05), C16(29.15), C17(56.78), C18(15.36), C19(11.85), C20(26.11), C21(18.70), C22(36.13), C23(23.05), C24(50.97), C25(28.76),C26(20.58),C27(20.19),C28(21.92),C29(11.96),C1'(170.20), C2'(17.58).

RESULTS AND DISCUSSION

No significant amount of diol, epoxide or diiodide compound was detected in the crude product.It is observed that the ease of formation of iodohydrins varies with the metal ion change and the anion change as shown in Table-1. The study clearly shows that the formation of iodohydrins takes place in presence of transition metal ions. $Cu(OAc)_2$ was observed to be most efficient giving highest yield, while $Fe_2(SO_4)_3$ is in close contest with it. The proposed methodology is simple, the reagents employed are cheap and easily available and furthermore, there is no need of special techniques.The detailed discussion and characterization of compounds is illustrated with I_2-H_2O-$Cu(OAc)_2$-1,4-dioxane combination as the suitable representative example.

CONCLUSION

We conclude that the above results as well as the mild reaction conditions which provide the product (3a or 4a) from their respective olefins (1&2) make the method highly useful.

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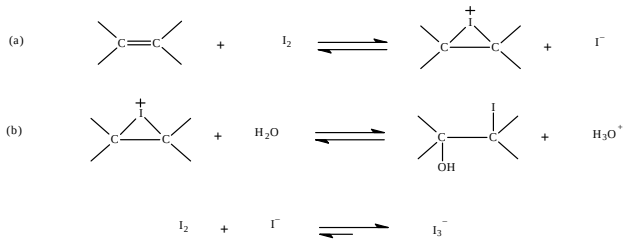
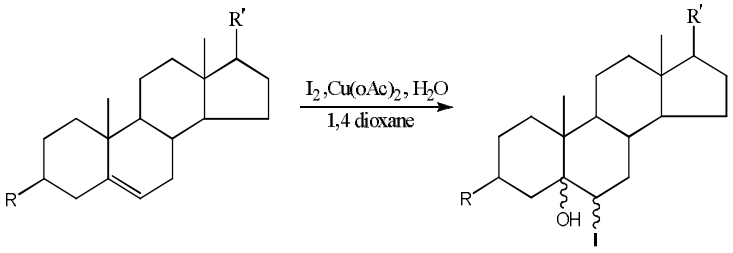


Scheme 1



	R	R'
(1)	OAc	C_8H_{17}
(2)	OAc	$C_{10}H_{21}$

	R	R'
(3a)	OAc	C_8H_{17} 5β 6 β
(3b)	OAc	C_8H_{17} 5α 6α
(3c)	OAc	C_8H_{17} 5α 6 β
(3d)	OAc	C_8H_{17} 5β 6 α
(4a)	OAc	$C_{10}H_{21}$ 5 α 6 β
(4b)	OAc	$C_{10}H_{21}$ 5β 6 β
(4c)	OAc	$C_{10}H_{21}$ 5α 6α
(4d)	OAc	$C_{10}H_{21}$ 5β 6 α

Table 1: Effect of salts on the reaction of steroidal olefins and iodine in aqueous 1,4-dioxane.

Metal salts	(1)		(2)	
	Reaction Time (hr)	% Yield	Reaction Time (hr)	% Yield
$Cu(OAc)_2$	1	75	4	90
NaOAc	2	35	4	42
$Pb(OAc)_2$	3	40	5	35
$CuSO_4$	1	35	5	38
$CdSO_4$	2	45	5	45
$ZnSO_4$	2	38	6	37
$FeSO_4$	120	15	120	22
$Fe_2(SO_4)_3$	1	70	4	89
$AgNO_3$	8	20	6	30

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