Aziridination of methyl long-chain alkenoates using chloramine-T

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Methyl long-chain alkenoates on treatment with chloramine-T [*N*-chloro-*N*-sodio-*p*-toluenesulfonamide] resulted in the formation of the corresponding aziridines in moderate yields. The *N*-substituted aziridine derivatives based on methyl undec-10-enoate (**1**), methyl *(Z)*-octadec-9-enoate (**3**) and methyl (*9Z,*12*R*)-12-hydroxyoctadec-9-enoate (**5**) have been synthesised under mild reaction conditions. The products were characterised using micro-analytical and spectral data.

Keywords: methyl long-chain alkenoates, chloramine-T, N-substituted aziridines

Aziridines are saturated three-membered nitrogen containing heterocycles which represent the first and simplest of all the small ring systems. They have great synthetic utilities toward number of reagents and can be converted into a wide variety of functionalised compounds by undergoing stereospecific and regioselective nucleophilic ring opening and ring expansion reactions.[1,2] Aziridines are reported to show many interesting biological properties.[3-5] Literature reports show that they are also the versatile building blocks for the synthesis of many important molecules like amino acids,[6] alkaloids,[7] β-lactams,[8] azinomycins,[9] mitomycins and azacycles.[10] Interest in the biological activities of aziridines and their utility as a synthetic intermediate has resulted in various synthetic procedures[11-18] for introducing a three-membered nitrogen heterocycle into a hydrocarbon chain.

However long-chain fatty acids containing N-heterocycles are not found in nature.[19] The aziridine derivatives of fatty acids have attracted great interest because of their significant biological properties and synthetic potential.[20] Numerous methods[19-25] have been developed to prepare the fatty aziridines but there is still a need for a new and easy method for their preparation. Keeping in mind the biological and synthetic potential of the aziridines we have tried to prepare the aziridine derivatives of internal and terminal olefinic fatty esters, which can further be used as intermediates for the synthesis of highly functionalised fatty compounds and can be tested for their biological activities. With regard to the reagent we have taken chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide), which serves as an oxidising agent as well as a source of nitronium cation and/or nitronium anion and is extensively used in analytical chemistry.[26] It has been found that chloramine-T is commonly used as a nitrogen source[12,16-18] for the aziridination process. We have carried out the aziridination of olefinic fatty esters adopting the procedure given by Ando *et al*[12] using chloramine-T as a nitrogen source and iodine as a catalyst. The reaction proceeded under mild conditions and the resulting compounds were obtained in good yield.

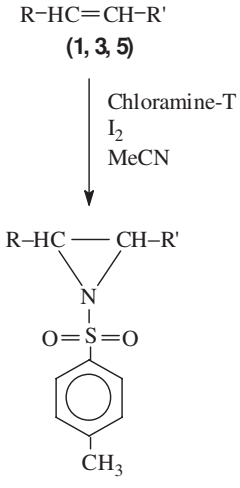
Results and discussion

Methyl undec-10-enoate (**1**), methyl (*Z*)-octadec-9-enoate (**3**) and methyl (9*Z*, 12*R*)-12-hydroxyoctadec-9-enoate (**5**) were converted into the corresponding aziridines (**2, 4, 6**) using chloramine-T in presence of iodine as a catalyst (Scheme 1).

IR spectrum of the product obtained from methyl undec-10-enoate (**1**) showed characteristic band for aziridine ring at 1323 cm^{-1} along with bands at 1163 cm^{-1} and 1733 cm^{-1} for the SO_2 and ester carbonyl group respectively. ^{1}HNMR spectrum displayed two doublets at δ 7.82 and 7.33 (J = 8.1 *Hz* for each doublet) for the aromatic ring protons. A sharp singlet at δ 3.67 was recorded for the three protons of ester group. The other three protons of the aziridine ring were showing a multiplet centred at δ 2.67. A singlet at δ 2.45 was observed for the methyl group protons attached to aromatic ring. These data suggested the product (**2**) as 2-[8-(methoxycarbonyl)octyl]-1-(*p*-toluenesulfonyl)aziridine. The MS of **2** corroborated the suggested structure by showing the structure supporting characteristic fragmentations. Prominent mass ions were observed at *m/z* 197 (α-cleavage to the aziridine ring), 210 and 224 (β- and γ- cleavages to the aziridine ring respectively), and 183 (M–$CH(CH_2)_9COOCH_3$). Other structure revealing peaks are given in the experimental section.

A similar reaction of methyl (*Z*)-octadec-9-enoate (**3**) yielded the corresponding aziridine (**4**, Scheme 1). ^{1}H NMR peaks at δ 7.82, 7.32 and 2.77 confirm the presence of aziridine ring in the molecule. Detailed spectral data are given in the experimental section. On the basis of these spectral data, compound **4** was assigned as *cis*-2-[7-(methoxycarbonyl)heptyl]-3-octyl1-(*p*-toluenesulfonyl)-aziridine. The position of aziridine ring in the molecule was further confirmed by the diagnostic peaks at *m/z* 339 and 296 in the MS.

Reaction of methyl (9*Z*,12*R*)-12-hydroxyoctadec-9-enoate (**5**) with chloramine-T (Scheme 1) resulted in the formation of the product (**6**) which was characterised as *cis*-1-(*p*-toluenesulfonyl)-2-[7-(methoxycarbonyl)heptyl]-3-[(*R*)-2-hydroxyoctyl]aziridine on the basis of elemental



	1/2	3/4	5/6
R	H	$CH_3(CH_2)_7$	$CH_3(CH_2)_5CHOHCH_2$
R'	$(CH_2)_8COOCH_3$	$(CH_2)_7COOCH_3$	$(CH_2)_7COOCH_3$

Scheme 1 Formation of fatty aziridines.

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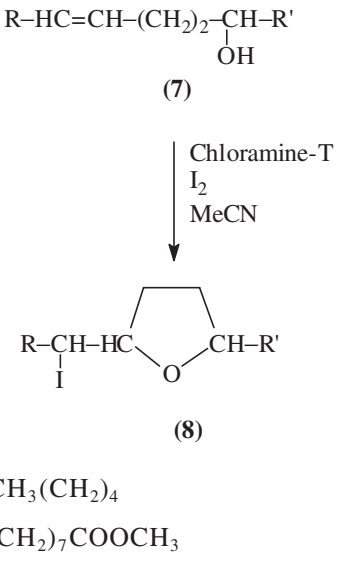

R = $CH_3(CH_2)_4$

R' = $(CH_2)_7COOCH_3$

Scheme 2 Formation of methyl 13-Iodo 9,12-epoxyoctadecanoate (**8**).

analysis and spectral data. MS of **6** was fully supporting its structure. Higher yield of this aziridine may be attributed to the increased stabilisation of the intermediate iodonium cation by the hydroxyl function.

A similar type of reaction of methyl (*9R,12Z*)-9-hydroxyoctadec-12-enoate (**7**) with chloramine-T does not result into its corresponding aziridine (**8**, Scheme 2). The product (**8**) moved above the starting compound (**7**) on the TLC plate. This information suggested the formation of a less polar compound than the starting material. It gave positive Beilstein test indicating the presence of a halogen in the molecule. The IR spectrum did not show any peak in the region of hydroxy group, rather a diagnostic band at 1169 cm^{-1} for 1,4-epoxide ring was observed along with absorption at 1023, 1091 and 935 cm^{-1} for ether linkage. A weak band at 561 cm^{-1} was assigned to C–I linkage. ^{1}H NMR spectrum exhibited a multiplet centred at δ 4.09 for a methane proton of C13 carbon attached to iodo group. Two more multiplets centered at δ 3.88 and 3.75 were observed for C9 and C12 methine protons of epoxide ring in the molecule. Four methylene protons of C10 and C11 of the epoxide ring gave a multiplet centered at δ 1.76. The structure assigned to **8** from these spectral data was methyl 13-iodo-9,12-epoxyoctadecanoate. MS of **8** further confirmed its five-membered cyclic structure. An intense peak at *m/z* 311 (M–I) confirmed the presence of iodine in the molecule. Positions of the constituent functional groups *i.e.* iodo and 1,4-epoxy were confirmed by the diagnostic fragments at *m/z* 211, 281, 227 and 295.

Formation of the five-membered cyclic product can be explained as a result of neighbouring group participation of the hydroxyl group. It is generally observed that intramolecular reactions dominate on intermolecular reactions and it was evident in our present work also. The intramolecular nucleophilicity of the λ-hydroxyl group competes successfully resulting in the formation of a five-membered cyclised product (**8**). This observation was also in accordance with 'Rules for ring closure' by Baldwin.[27]

Experimental

Undec-10-enoic and (*Z*)-octadec-9-enoic acids were obtained commercially from Fluka chemicals (Switzerland). (9*Z*,12*R*)-12-hydro-xyoctadec-9-enoic (ricinoleic) and (9*R*,12*Z*)-9-hydroxyoctadec-12-enoic (isoricinoleic) acids were isolated from the natural sources i.e. from *Ricinus communis* and *Wrightia tinctoria* seed oils respectively following the Gunstone's partition method.[28] General (GR) grade of solvents were employed for the extraction purposes and when required solvents were dried and distilled before use.

Chromatographic techniques and the instruments used for the spectral studies were similar as described in our earlier paper.[29] Methyl esters of the corresponding acids were prepared by using catalytic amount of sulfuric acid in absolute methanol.

General procedure for the aziridination of long-chain methyl esters: The methyl ester of the olefinic fatty acid (**1** or **3** or **5** or **7**, 2 mmol each) in acetonitrile (5 ml) was added to a solution of iodine (0.1 mmol), chloramine-T (1 mmol) and naphthalene (0.1 mmol) in acetonitrile (10 ml). The reaction mixture was allowed to stir at room temperature for 28 h. The progress of the reaction was monitored on TLC plate and at the completion the reaction mixture was extracted with dichloromethane (3 × 20 ml). Organic extract was washed with water (3 × 15 ml) and brine (20 ml), dried over anhydrous sodium sulfate. The solvent was removed under pressure to obtain the crude products, which on purification by column chromatography afforded the product (**2** or **4** or **6** or **8**).

2-[8-(Methoxycarbonyl)octyl]-1-(p-toluenesulfonyl)aziridine (**2**): Purification of crude product over a column of silica gel using petroleum ether-diethyl ether (88:12, v/v) as the eluting solvent gave a colourless liquid (**2**, 0.52g, 70%).

(Found: C, 63.85; H, 8.21; N, 4.09%; $C_{19}H_{29}NO_4S$ requires: C, 62.12; H, 7.90; N, 3.81%). IR, cm^{-1}: 1323 (C–N), 1163 (SO_2) and 1733 ($COOCH_3$). ^{1}H NMR, δ: 7.82 d (2H, *J* = 8.1 Hz, aromatic ring protons), 7.33 (2H, *J* = 8.1 Hz, aromatic ring protons), 3.67 s (3H, $COOCH_3$), 2.67 m (3H, aziridine ring protons), 2.45 s (3H, $ArCH_3$), 2.30 t (2H, *J* = 6.0 Hz, $-CH_2$ α to carbonyl group) 1.57 brm (protons β to carbonyl group and α to aziridine ring), 1.25 brs (chain $-CH_2-$). MS, *m/z* (%):

M^+ 367(2), M+1 368(100), M+2 369(23), 353(4.2), 336(92), 308(4), 238(6.3), 224(18.8), 212(16.6), 210(6), 197(8.3), 196(4), 184(37.5), 183(4.2), 172(14.6), 171(6.3) and 155(25).

cis-2-[7-(methoxycarbonyl)heptyl]-3-octyl-1-(p-Toluenesulfonyl)-aziridine (**4**): Compound (**4**) was purified through column chromatography with light petroleum ether-diethyl ether (82:18, v/v) as the solvent. Purification gave a colourless liquid (0.59g, 64%).

(Found: C, 68.95; H, 10.56; N, 3.75%; Calculated for $C_{26}H_{43}NO_4S$: C, 67.09; H, 9.24; N, 3.01%). IR, cm^{-1}: 1326(C–N), 1161(SO_2), 1740 ($COOCH_3$). ^{1}H NMR, δ: 7.82 d (2H, *J* = 8.4 Hz, aromatic ring protons), 7.32 d (2H, *J* = 8.4 Hz, aromatic ring protons), 3.67 s (3H, $COOCH_3$), 2.77 m (2H, aziridine ring protons, C9 and C10 methine protons), 2.44 s (3H, $ArCH_3$), 2.30 m (2H, $-CH_2$ α to carbonyl group), 1.57 brm (6H, 2 × $-CH_2$ α to aziridine ring and $-CH_2$ β to esters carbonyl), 1.24 brs (chain $-CH_2-$), 0.88 distorted t (3H, terminal $-CH_3$). MS, *m/z* (%): M^+ 465(2.2), M+1 466(100), M+2 467(31.3), 434(23), 353(8.3), 352(12.1), 340(12.5), 339(3.9), 311(14.6), 310(48), 308(25), 296(9.8), 252(4.2), 198(8.3), 197(6.3), 196(6), 185(6.2), 184(10.4), 182(4), 155(81.2) and 154(25.7).

cis-1-(p-Toluenesulfonyl)-2-[7-(methoxycarbonyl)heptyl]-3-[(R)-2-hydroxyoctyl]aziridine (**6**): Purification of crude compound by column chromatography with petroleum ether-diethyl ether (75:25, v/v) as the eluent gave the colourless liquid aziridine (**6**, 0.79g, 81%).

(Found: C, 65.12; H, 9.05; N, 3.49%; $C_{26}H_{43}NO_5S$ requires: C, 64.86; H, 8.94; N, 2.91%). IR, cm^{-1}: 3530 (OH), 1160 (C–N), 1322 (SO_2) and 1736 ($COOCH_3$). ^{1}H NMR, δ: 7.82 d (2H, *J* = 8.2 Hz, aromatic ring protons), 7.32 d (2H, *J* = 8.2 Hz, aromatic ring protons), 3.76 m (1H, C12 methine proton attached to hydroxyl group), 3.67 s (3H, $COOCH_3$), 2.95 m (1H, proton of hydroxyl group, CHO*H*, D_2O exchangeable), 2.73 m (2H, aziridine ring protons *i.e.* C9 and C10), 2.43 s (3H, $ArCH_3$), 1.55 brm ($-CH_2$ α to aziridine ring and β to carbonyl group), 1.26 brs (chain $-CH_2-$) and 0.88 distorted t (3H, terminal $-CH_3$). MS, *m/z* (%): M^+ 81 (2.2), M+1 482(31.2), M+2 483(14.5), 450(14.6), 391(8.3), 366(6.3), 3.43(2.1), 338(18.8), 327(12.5), 326(4.0), 324(4.2), 311(10.4), 309(14.0), 307(6.0), 257(8.0), 256(4.2), 212(22.9), 198(16.6), 197(19.0), 185(17.0), 184(10.0), 171(16.8), 170(10.2), 157(23.0) and 155(29.1).

Methyl 13-iodo-9,12-epoxyoctadecanoate (**8**): Compound (**8**) when purified by column chromatography using petroleum ether-diethyl ether (90:10, v/v) as the solvent gave the colourless liquid (0.69g, 75%).

(Found: C, 53.98; H, 8.26%; $C_{19}H_{35}O_3I$ requires: C, 52.05; H, 7.99%). IR, cm^{-1}: 1741($COOCH_3$), 1169(1,4–epoxide), 1023, 1091, and 935 (ether linkage) and 561(C–I). ^{1}H NMR, δ: 4.09 m (1H, methine proton of C13 attached to iodo group), 3.88 m (1H, methine proton of C12 of epoxy ring), 3.75 m (1H, methine proton of C9 of epoxy ring), 3.66 s (3H, $COOCH_3$), 2.30 t (2H, *J* = 7.5 Hz, $-CH_2$ α to carbonyl group), 2.09 m (2H, $-CH_2$ α to iodo group), 1.76 m (4H, four

methylene protons of C10 and C11 of the epoxy ring), 1.57 m (–CH_2 α to epoxy ring and β to carbonyl group), 1.30 brs (chain –CH_2–) and 0.89 distorted t (3H, terminal –CH_3). MS, *m/z* (%): M^+ 438(11), M+1 439(77.1), M+2 440(16.6), 311(100), 310(16.4), 309(2.1), 295(4.2), 293(81.2), 281(10.4), 279(52.0), 227(18.7), 211(9.8), 209(8.3), 195(16), 177(6.2), 154(14.6) and 149(27.0).

We thank the Chairman, Department of Chemistry, Aligarh Muslim University, Aligarh for providing all the necessary research facilities and Central Drug Research Institute (CDRI), Lucknow, India for spectral studies.

Received 3 January 2005; accepted 9 March 2005
Paper 05/2985

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