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Preparation of Ethenyl and Oxiranol Carbamate and their (2-²H₂)-Derivatives Using Selenium Chemistry; Thermolysis of Oxiranol Carbamate and Reaction with Adenosine

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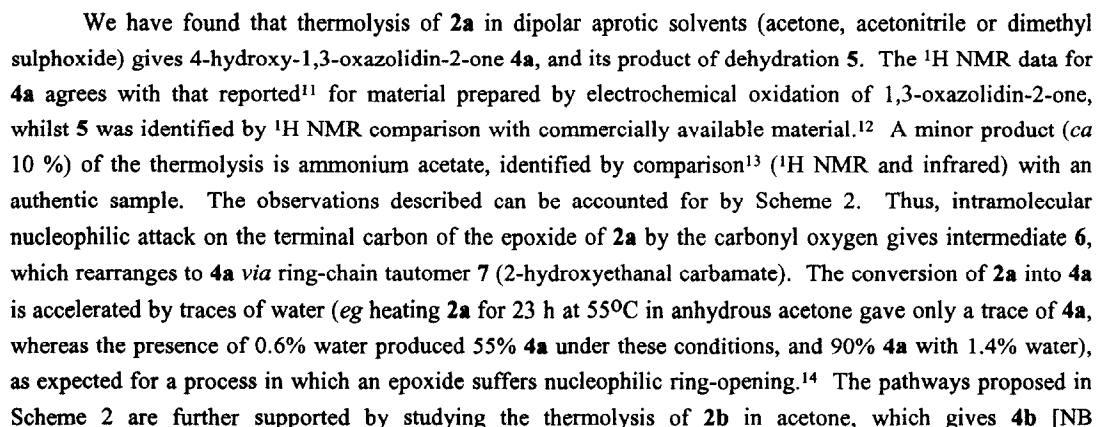*Key Words*: Vinyl carbamate, oxirane, urethane, selenium, dimethyldioxirane.

Abstract: Ethenyl carbamate was obtained by selenoxide fragmentation of 2-phenylselenylethyl carbamate. Base-catalysed exchange of ethyl phenylselenylacetate in methanol-OD gave methyl [²H₂]phenylselenylacetate from which [2-²H₂]ethenyl carbamate and [2-²H₂]oxiranol carbamate were derived. Thermolysis of oxiranol carbamate in *eg* acetone gave 4-hydroxy-1,3-oxazolidin-2-one and 3*H*-1,3-oxazol-2-one.

We have recently reported the preparation of ethenyl carbamate (**1a**, vinyl carbamate) using di-(4-methoxyphenyl)methyl ('dimethoxybenzhydryl', DMB) as an *N*-protecting group for the carbamoyl function.[1] This utilised a selenoxide fragmentation to generate the ethenyl function, with the DMB group serving to facilitate isolation of product. In connection with mechanistic studies of the initiation of carcinogenesis by ethyl carbamate and its putative metabolites ethenyl carbamate **1a** and oxiranol carbamate (epoxyvinyl carbamate, **2a**),[2,3] we required a synthesis of these compounds specifically labelled with deuterium at the 2-position of the ethenyl and oxiranol groups (compounds **1b** and **2b**, respectively). We have now found a simple route (see Scheme 1) to **1a** and hence **2a**, which utilises oxidation with dimethyldioxirane[4] to achieve the selenide/selenoxide conversion and obviates the need for *N*-protection. Furthermore, the corresponding deuterium-labelled compounds **1b** and **2b** (Scheme 1) are accessible by a base-catalysed exchange on ethyl 2-phenylselenylacetate, facilitated by the selenium atom.

Reaction of the phenylselenyl anion with ethyl 2-bromoacetate gave ethyl 2-phenylselenylacetate (*cf* ref 5), which was converted (DIBAL reduction) into 2-phenylselenylethanol and hence by the method of ref 6 into carbamate **3a**. Oxidation of **3a** with dry dimethyldioxirane in acetone gave a selenoxide intermediate, which fragmented to ethenyl carbamate **1a** on refluxing in dry tetrahydrofuran containing suspended sodium carbonate. Oxidation of **1a** using dimethyldioxirane (NB the use of this reagent for this purpose was described in ref 7) gave **2a**. Using 2-phenylselenylethanol prepared directly from the phenylselenyl anion by reaction with 2-bromoethanol (in the manner described[8] using oxirane), we have routinely prepared ethenyl carbamate in 60% overall yield (three stages from diphenyldiselenide). Experimentals details for this procedure are given in the **References and Notes.**[9]

A solution of ethyl phenylselenylacetate in methanol-OD containing 1 mol equiv triethylamine underwent within 24 h/35 °C exchange at the methylene group (flanked by the selenium and carbonyl) and transesterification, to give methyl [C²H₂]phenylselenylacetate. This process was repeated in fresh methanol-OD/triethylamine to give methyl [C²H₂]phenylselenylacetate containing no detectable methylene H by ¹H NMR analysis. The ester was converted into [²H₂]ethenyl carbamate **1b** and [²H₂]oxiranol carbamate **2b** *via*

3b in the manner described above for the corresponding unlabelled compounds (see **References and Notes**[9,10] for procedures). Compounds **1b** and **2b** were shown to be essentially completed deuteriated at their methylene group by ^{1}H and ^{2}H NMR analysis.

Scheme 1: Preparative Routes to Ethenyl and Oxiranol Carbamate and Their (2-^2H_2)-Derivatives.

We have found that thermolysis of **2a** in dipolar aprotic solvents (acetone, acetonitrile or dimethyl sulphoxide) gives 4-hydroxy-1,3-oxazolidin-2-one **4a**, and its product of dehydration **5**. The ^{1}H NMR data for **4a** agrees with that reported[11] for material prepared by electrochemical oxidation of 1,3-oxazolidin-2-one, whilst **5** was identified by ^{1}H NMR comparison with commercially available material.[12] A minor product (*ca* 10 %) of the thermolysis is ammonium acetate, identified by comparison[13] (^{1}H NMR and infrared) with an authentic sample. The observations described can be accounted for by Scheme 2. Thus, intramolecular nucleophilic attack on the terminal carbon of the epoxide of **2a** by the carbonyl oxygen gives intermediate **6**, which rearranges to **4a** *via* ring-chain tautomer **7** (2-hydroxyethanal carbamate). The conversion of **2a** into **4a** is accelerated by traces of water (*eg* heating **2a** for 23 h at 55°C in anhydrous acetone gave only a trace of **4a**, whereas the presence of 0.6% water produced 55% **4a** under these conditions, and 90% **4a** with 1.4% water), as expected for a process in which an epoxide suffers nucleophilic ring-opening.[14] The pathways proposed in Scheme 2 are further supported by studying the thermolysis of **2b** in acetone, which gives **4b** [NB

dideuteriation at C-5 (^{1}H NMR analysis)] and ammonium dideuterioacetate (characterised by ^{1}H and ^{2}H NMR). A possible mechanism of formation of ammonium acetate from **2a** requires a 1,2-hydride shift in **6** (from C-4 to C-5) and this is supported by the finding that **2b** gives ammonium dideuterioacetate. Miller *et al*^{2} have suggested that **2a** could decompose by NIH shifts leading to **7** and acetyl carbamic anhydride. We have shown an alternative pathway for the formation of **7** (which has been proved *not* to involve a 1,2-hydride shift). We have also shown that acetic acid is formed as its ammonium salt, possibly *via* a 1,2-hydride shift.

Scheme 2: Conversion of Oxiranol Carbamate into 4-Hydroxy-1,3-oxazolidin-2-one and Ammonium Acetate.
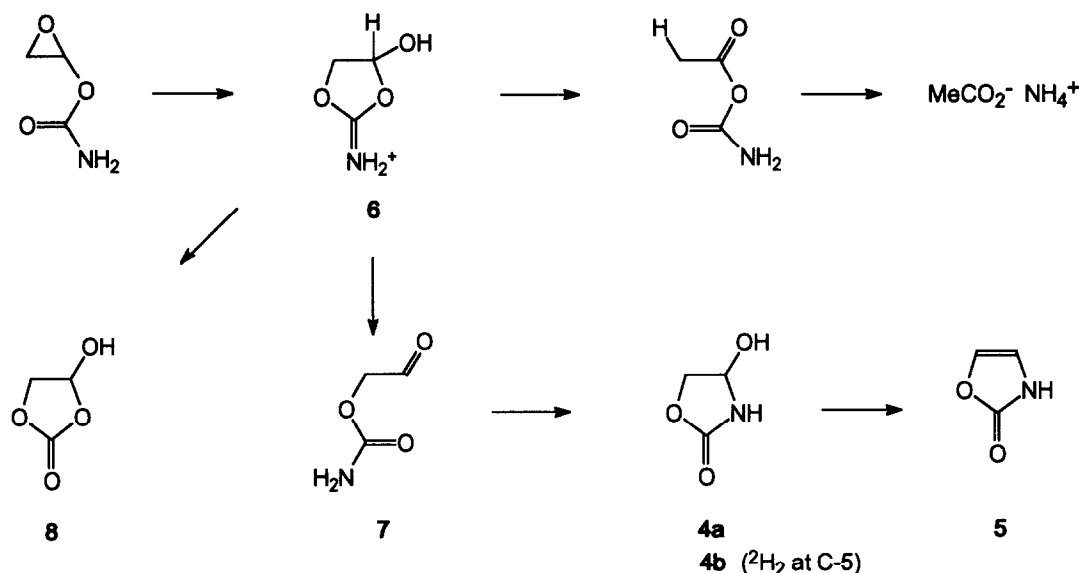
Miller and his coworkers^{2,7} reported that oxiranol carbamate **2a** decomposes in water (pH 7.4 phosphate buffer) with a half-life of 10.5 minutes at 37 ^oC, as assessed by reaction of the remaining **2a** with 4-(*p*-nitrobenzyl)pyridine. Using ^{1}H NMR for monitoring the decomposition, we found that the major product from **2a** in D_2O (3 h/20 ^oC) is 2-hydroxyethanal (as its hydrate; NB this product was isolated by Miller *et al*^{2} as its 2,4-dinitrophenylhydrazone) with a trace of **4a**. The formation of 2-hydroxyethanal from **2a** in pure water can be explained as the result of direct hydrolysis of the epoxide ring. Alternatively, capture of intermediate **6** at C-2 by water can be postulated (see Scheme 2) leading to **8**, *via* a tetrahedral intermediate that loses ammonia. This decomposes to 2-hydroxyethanal and carbon dioxide.

It has been reported^2 that **2a** reacts with adenosine in water to give 5-10% 1,N^6-ethenoadenosine **9a**, and suggested that if such a reaction occurs in DNA then this might explain how oxiranol carbamate initiates cancer. We have studied the formation of 1,N^6-ethenoadenosine from adenosine and **2a** in d^6-dimethylsulphoxide at room temperature by ^{1}H NMR. New resonances appear at δ 7.68 (d, *J* 1.5 Hz) and 8.19 (d, *J* 1.5 Hz) which are assigned to H-8 and H-7, respectively, of 1,N^6-ethenoadenosine **9a** (integration showed *ca* 3% **9a** after 17h, and 8% after 117h, at which point all of **2a** had been consumed, mostly by conversion into **4a** + **5**; further production of **9a** then ceases). A similar reaction of adenosine with **2b** gave **9b** [δ 7.68 (s, H-

8); for assignment of H-7 and H-8 in **9a** see ref 15]. This suggests a mechanism of formation of **9a/9b** (see Scheme 3) in which there is initial nucleophilic attack by N-1 of adenosine on the terminal epoxide carbon (of **2a/2b**), analogous to that proposed for reaction of adenosine with chloro- and bromo-oxirane.[15]

Scheme 3: Mechanism of Formation of [7-²H]1,N⁶-Ethenoadenosine **9b** from **2b**.
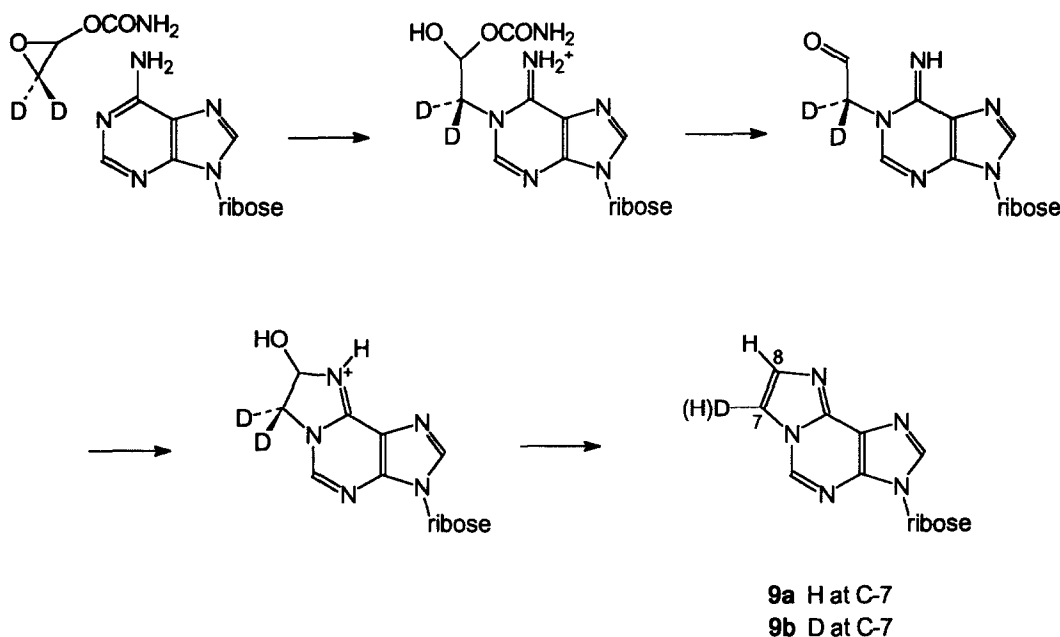
9a H at C-7
9b D at C-7

Acknowledgement

References and Notes

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3   F P Guengerich and D H Kim, *Chem Res Toxicol*, 1991, **4**, 413.

4   R W Murray, *Chem Revs*, 1989, **89**, 1187. We prepare dimethyldioxirane by a simplification of the
     method described by R W Murray and R Jeyeraman, *J Org Chem*, 1985, **50**, 2847:

Dimethyldioxirane
A 1 L three necked round bottom flask containing a mixture of HPLC grade water (127 ml), HPLC grade acetone (96 ml, 1.31 mol), and sodium bicarbonate (72 g, 0.86 mol) was equipped with a mechanical stirrer, a Vigreux condenser and a stopper. The exit of the condenser was connected to the side arm of a Cardice condenser (-78 °C). The bottom exit of the Cardice condenser was attached to a 100 ml one neck round bottom receiving flask which was placed in a Cardice-acetone bath. Oxone (155 g, 0.255 mol) was added in 5 portions at three minute intervals from a bulb rotated *via* its ground glass joint, while stirring the mixture vigorously at room temperature. After the last addition, a vacuum (60-100 mmHg) was applied, and the

yellow effluent solution of dimethyldioxirane (60-70 ml; 0.06-081 M, molarity determined as in ref 4) was collected in the receiving flask. The dimethyldioxirane solution was dried with 4Å powdered molecular sieves and stored at -20 °C.

5   K B Sharpless and R F Lauer, *J Am Chem Soc*, 1973, **95**, 2697 and K B Sharpless, R F Lauer, and A Y
     Teranishi, *ibid*, p 6137.

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9   **Ethenyl carbamate (SAFETY NOTE: this compound and oxiranol carbamate are both suspect human carcinogens)**.- Sodium phenylselenide was reacted with 2-bromoethanol essentially as described[8] for its reaction with oxirane to give a crude product that was purified by Kugelrohr distillation (0.01 mmHg, oven temperature 80-90 °C) to yield 2-phenylselenylethanol as a yellow oil (88%): δ_H (200 MHz; $CDCl_3$) 2.76 (1 H, t, J 6 Hz, OH), 3.03 (2 H, t, J 6 Hz, PhSeCH_2), 3.72 (2 H, dt, CH_2OH, J 6 Hz), 7.20 (3 H, m, 3 x PhH), 7.60 (2 H, m, 2 x PhH).

Using the method of ref 6, 2-phenylselenylethanol was converted into its carbamate **3a**: 87%, mp 64-66 °C; δ_H (200 MHz, $CDCl_3$) 3.07 (2 H, t, J 7 Hz, SeCH$_2$), 4.26 (2 H, t, J 7 Hz, CH$_2$O), 5.03 (2 H, br s, NH$_2$), 7.21 (2 H, m, 2 x PhH), 7.60 (3 H, m, 2 x PhH); m/z (ei ms) 245 (M^+, 77%), 185 (100), 157 (40) [Found: C, 44.08; H, 4.49; N, 5.71. $C_9H_{11}NO_2Se$ requires C, 44.27; H, 4.54; N, 5.74%].

Compound **3a** was converted into ethenyl carbamate in the manner described below for preparing **1b** from **3b** (**References and Notes**[10]).

NB   All new compounds described in this paper were chromatographically homogeneous (TLC) and gave analytical/spectroscopic data (^{1}H and ^{13}C NMR, IR and MS; combustion analyses for crystalline compounds in the unlabelled series) in accordance with their assigned structure.

10   **Ethyl phenylselenylacetate**.- Sodium borohydride (3.2 g, 0.086 mol) was added slowly in small portions to a stirred solution of diphenyl diselenide (12.0 g, 0.038 mol) in absolute ethanol (200 ml), under nitrogen. After a short time the yellow solution became colourless, and ethyl bromoacetate (7.7 ml, 0.069 mol) was added dropwise. The reaction mixture was stirred at room temperature for 8 h. The salts were filtered off and the filtrate was concentrated *in vacuo*. Water (50 ml) was added to the residue and the product was extracted into dichloromethane (4 x 50 ml). The combined extracts were dried (Na$_2$SO$_4$), and concentrated under reduced pressure to give a bright yellow oil, which was purified by Kugelrohr distillation (0.03 mmHg, oven temperature 70 °C) to give the title compound as a yellow oil (8.68 g, 94%): δ_H (200 MHz; $CDCl_3$) 1.17 (3 H, t, J 7.1 Hz, CH$_2$CH_3), 3.48 (2 H, s, PhSeCH_2), 4.10 (2 H, q, J 7.1 Hz, CH_2CH$_3$), 7.21 (3 H, m, 3 x PhH), 7.60 (2 H, m, 2 x PhH); δ_C (50.3 MHz, $CDCl_3$) 14.1, 27.6, 61.4, 127.9, 129.2, 133.5, 134.5, 170.9.

Methyl [^{2}H$_2$]phenylselenylacetate.- Triethylamine (3.8 ml, 0.027 mmol) was added to a solution of ethyl phenylselenylacetate (6.62 g, 0.027 mol) in methanol-OD (53.0 ml, 1.304 mol) under nitrogen. The solution was kept at 35 °C for 24 h. The solvent was removed *in vacuo* to give an oily residue, which was redissoved in fresh methanol-OD (53.0 ml) containing triethylamine (3.8 ml) and left at 35 °C for 24 h. The solvent was removed and the residual oil was purified by Kugelrohr distillation (0.02 mmHg, oven temperature 80 °C) to give the title compound as yellow oil (5.36 g, 86%): δ_H (200 MHz; $CDCl_3$) 3.55 (3 H, s), 7.21 (3 H, m, 3 x PhH), 7.50 (2 H, m, 2 x PhH); δ_D [46.1 MHz; acetone ($CDCl_3$)] 3.60 (br s, CD$_2$); m/z (ei) 232 (M^+, 100%), 173 (76), 157 (62), 93 (90), 77 (51).

[2-^{2}H$_2$]2-Phenylselenylethanol

To a stirred solution of methyl [^{2}H$_2$]phenylselenylacetate (11.025 g, 0.048 mol) in dry tetrahydrofuran (40 ml) under nitrogen at room temperature was added di-isobutylaluminum hydride in toluene (1M, 108 ml, 0.106 mol). The reaction mixture was stirred for 3.5 h before quenching at -20 °C with a mixture of methanol (100 ml) and distilled water (80 ml). The resulting suspension was filtered and the filter-cake was washed with dichloromethane. The filtrate was shaken and the organic layer was separated and dried (Na$_2$SO$_4$). The solvent was removed and the residual oil was purified by Kugelrohr distillation (0.02 mmHg, oven temperature 80 °C) to give a golden yellow oil (8.74 g, 90%): δ_H (200 MHz; $CDCl_3$) 2.99 (1 H, br s, OH), 3.72 (2 H, s,

CH₂), 7.21 (3 H, m, 3 x PhH), 7.50 (2 H, m, 2 x PhH); δ_D [46.1 MHz; acetone (CDCl₃)] 3.20 (br s, SeCD₂); δ_C (50.3 MHz; CDCl₃) 30.7 (quintet, J_{C-D} 25 Hz); m/z (ei) 204 (M^+, 13 %), 158 (21), 93 (16).

[²H₂]2-(Phenylselenyl)ethyl carbamate.- Trifluoroacetic acid (4.1 ml, 0.053 mmol) was added slowly to a stirred mixture of 2-(phenylselenyl)ethanol (4.8 g, 0.024 mol) and sodium cyanate (3.4 g, 0.053 mol) in dichloromethane (30 ml), whereupon an exothermic reaction was observed. The reaction vessel was loosely stoppered, and left stirring overnight at room temperature. Distilled water (20 ml) was added and the mixture was extracted with dichloromethane (5 x 10 ml). The combined organic extracts were dried with Na₂SO₄, filtered, and the solvent was removed. The residual solid was recrystallized from hot water to give the title compound as a white solid (5.21 g, 88%), mp 66-68 °C: δ_H (200 MHz; CDCl₃) 4.20 (2 H, s), 4.74 (2 H, br s), 7.20 (3 H, m, 3 x PhH), 7.50 (2 H, m, 2 x PhH); δ_D [46.1 MHz; acetone (CDCl₃)] 3.24 (br s, SeCD₂); δ_C (50.3 MHz; CDCl₃) 25.3 (quintet, J_{C-D} 22 Hz); m/z (ei) 247 (M^+, 73%), 185 (100), 157 (60), 77 (62).

[2-²H₂]Ethenyl carbamate.- To a stirred solution of [²H₂]2-(Phenylselenyl)ethyl carbamate (1.0 g, 4.06 mmol) in dry acetone (10 ml) at room temperature was added dry dimethyldioxirane (110 ml of a 0.081 M solution, 8.92 mmol). The reaction mixture was stirred for 24 h after which the acetone was removed with a rotary evaporator, with the distillation flask immersed in ice-water. The resulting white solid [presumably the selenoxide of 2-(phenylselenyl)ethyl carbamate: δ_H (200 MHz; d₆-DMSO) 4.20 (2 H, t, SeOCH₂), 4.60 (2 H, t, CH₂OCO), 6.77 (2 H, br s, NH₂), 7.70 (3 H, m, PhH), 8.10 (2H, m, PhH)] was taken up in dry tetrahydrofuran (20 ml) and anhydrous sodium carbonate (2.16 g, 0.02 mol) was added. The mixture was refluxed at 65 °C for 3 h. The solid (containing NaOSePh) was filtered off and the filtrate was concentrated. The residual oil was chromatographed on silica gel [elution with dichloromethane followed by dichloromethane-methanol (98:2)] to give the title compound as a white solid (0.83 g, 78%), mp 63-66 °C; δ_H (200 MHz; d₆-acetone) 6.18 (2 H, br s, NH₂), 7.40 (1 H, m, J_{AX} 0.9 Hz, J_{BX} 2.0 Hz); δ_D (46.1 MHz; acetone) 4.54 (1 D, J_{AX} 1.0 Hz), 4.81 (1 D, d, J_{BX} 2.1 Hz) [cf for unlabelled ethenyl carbamate: δ_H (200 MHz; CDCl₃) 4.40 (1 H, dd, J_{AX} 6.3 Hz, J_{AB} 1.7 Hz), 4.70 (1 H, ddd, J_{BX} 14.0 Hz, J_{AB} 1.7 Hz), 5.30 (2 H, br s, NH₂), 7.10 (1 H, dd, J_{AX} 6.3 Hz, J_{BX} 14.0 Hz); δ_C (50.3 MHz; CDCl₃) 94.0 (quintet, J_{C-D} 25 Hz); m/z (ei) 89 (M^+, 46%), 46 (86), 44 (100).

[2-²H₂]Oxiranol carbamate.- To [2-²H₂]Ethenyl carbamate (68 mg, 0.76 mmol) in dry acetone (23 ml) freshly prepared dry dimethyldioxirane solution (21 ml of a 0.08 M solution, 2.2 equiv) was added over 3 min under nitrogen. The resulting solution was stirred at room temperature under nitrogen for 1 h. After complete consumption of the starting material, the acetone was removed *in vacuo* with the flask surrounded by ice-water. This gave a white crystalline solid (70 mg, 88%), which was pure oxiranol carbamate by ¹H NMR analysis: δ_H (200 MHz; d⁶-acetone) 5.50 (1 H, s), 6.32 (2 H, br s), δ_D [46.1 MHz; acetone (CDCl₃)] 2.88 (1 D, br s, D_B), 2.92 (1 D, br s, D_A).

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12   A sample of 3*H*-1,3-oxazol-2-one [27584-70-9] was obtained from the Aldrich Chemical Company; δ_H (d₆-DMSO) 6.75 (1 H, d, *J* 2 Hz, H-4), 6.86 (1 H, d, *J* 2.2 Hz, H-5).

13   **[2-²H₂]Ammonium acetate.-** δ_D [46.1 MHz; acetone (CDCl₃)] 2.42 (2 D, d, *J* 0.77 Hz).
Ammonium acetate- δ_H [d₆-acetone (D₂O), 200 MHz] 2.20 (3 H, s), v_{max} 3382, 1664, 1414 cm⁻¹.

14   R E Parker and B W Rockett, *J Chem Soc*, 1965, 2569.

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16   F P Guengerich, M Persmark, and W G Humphreys, *Chem Res Toxicol*, 1993, **6**, 635.