

Synthesis and ^1H NMR Spectroscopic Studies of Partially Deuterated *N*-Propionyl Derivative of Chiral Auxiliary Chiracamphox Spiro-Oxazolidin-2-One

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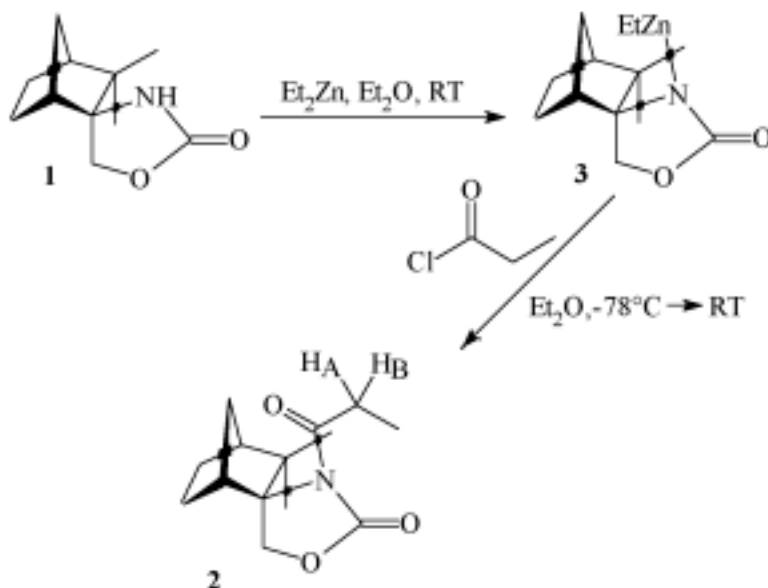
ABSTRACT. In order to distinguish between the prochiral methylene protons H_A and H_B in the *N*-propionyl derivative of the chiral auxiliary spiro-oxazolidin-2-one, the partial deuteration of one of these two protons was employed. A new method was employed for synthesis of the *N*-propionate partially deuterated derivative using lithium di-isopropyl amide (LDA) to form lithium enolate which was treated with AcOD to yield non-isolated mixture of both the *N*-propionyl derivative and its partially deuterated derivative. ^1H NMR studies of the product revealed that the partial deuteration was occurred and confirmed that the two diastereotopic protons H_A and H_B are distinguishable.

Introduction

One of the most successful chiral auxiliaries is the camphene-derived auxiliary, chiracamphox **1**^[1], which was synthesised by Banks *et al.*^[2,3] and is now commercially available. Functionalisation of chiracamphox **1** occurs readily upon treatment of its magnesium salt with an appropriate acid chloride. In each case, the adducts perform excellently in lithium enolate mediated alkylation and acylation reactions, boron enolate aldol reactions, Lewis-acid catalysed Diels-Alder reactions and in 1,4-conjugate additions with diastereomeric excess between 85 and 99% in all these reaction^[4,5].

The *N*-propionyl derivative **2** was synthesised by Banks *et al.*^[4,5] via different methods and afforded good yields. In order to increase the yield of the *N*-propionyl derivative **2**, an alternative method was employed for this purpose by

Sobahi^[6]. In essence, the chiral auxiliary **1** was treated with 1.1 equivalents of diethyl zinc at room temperature in anhydrous Et₂O to form an intermediate *N*-ethyl zinc salt **3**, which was then treated with excess of propionyl chloride. Thus, use of this procedure with **1** gave 100% yield of the *N*-propionyl derivative **2** as a colorless solid^[6] (Scheme 1).



SCHEME 1

Experimental

*Preparation of (5*S*)-(N-propionyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro [4.5] decan-3-one 2*

Literature method was used to prepare **2**^[6]. All physical and spectroscopic data for **2** were available in reference^[6]. High field NMR spectra were obtained on a Bruker Avance DPX-400 spectrometer operating at 400.13 MHz for ¹H.

*Preparation of partially deuterated derivative of (5*S*)-(N-propionyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro [4.5] decan-3-one 5*

A solution of LDA (1.32 mmol, 1.1 eq) was prepared by the dropwise addition of *n*-butyllithium (0.84 ml of 1.6 M solution, 1.32 mmol, 1.1 eq) to a solution of anhydrous di-isopropylamine (0.134 g, 1.32 mmol, 1.1 eq) in dry THF (15 ml) at 0°C under argon. The solution was stirred at 0°C for 30 minutes, cooled to -78°C and treated with a solution of *N*-propionyl derivative **2** (0.30 g, 1.20 mmol, 1 eq) in dry THF (10 ml). The reaction mixture was stirred at this

temperature for a further 30 minutes before addition of a solution of acetic acid-*d* AcOD ($\text{CH}_3\text{CO}_2\text{D}$) (0.147 g, 2.40 mmol, 2 eq) in dry THF (5 ml) *via* syringe. The reaction mixture was allowed to warm to room temperature and stirred under argon for four hours. THF was removed in *vacuo* and then the product was washed with saturated sodium bicarbonate solution (20 ml) and then extracted into dichloromethane (3×20 ml). The combined dichloromethane extracts were dried over magnesium sulfate and evaporated to dryness in *vacuo* to yield the product as a colorless gum which crystallised on standing to give non-isolated mixture (0.29 g, 97%) of the *N*-propionyl derivative **2** and its partially deuterated derivative **5**; mp 54-56°C; FTIR (nujol) ν_{max} 1780 (oxazolidinone C = O), 1705 (C = O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.33-4.00 (2 H, dd, $J = 9.1$ Hz, CH_2O), 2.99 (1H, dq, $J = 17.6, 7.3$ Hz, $\text{CH}_A\text{H}_B\text{CH}_3$), superimposed on 2.99-2.89 (1 H, qt, $J = 7.3, 2.7$ Hz, CH_AD), 2.80 (1H, dq, $J = 17.6, 7.3$ Hz, $\text{CH}_A\text{H}_B\text{CH}_3$), 2.75 (1 H, d, $J = 10.7$ Hz, CH), 2.68 (1 H, s, CH), 1.83 (1 H, m, CH), 1.59-1.44 (4 H, m, 2CH_2), 1.38-1.28 (1 H, d, $J = 10.4$ Hz, CH), 1.13 (3 H, s, CH_3), 1.05 (3 H, t, $J = 7.3$ Hz, CH_3CH_2), superimposed on 1.04 (3 H, d, $J = 7.3$, CH_ADCH_3), 0.98 (3 H, s, CH_3) ppm; MS (FAB) m/z 135(64%), 136(48), 196(46), 197(42), 252(40 M + H), 253(49 MD + H).

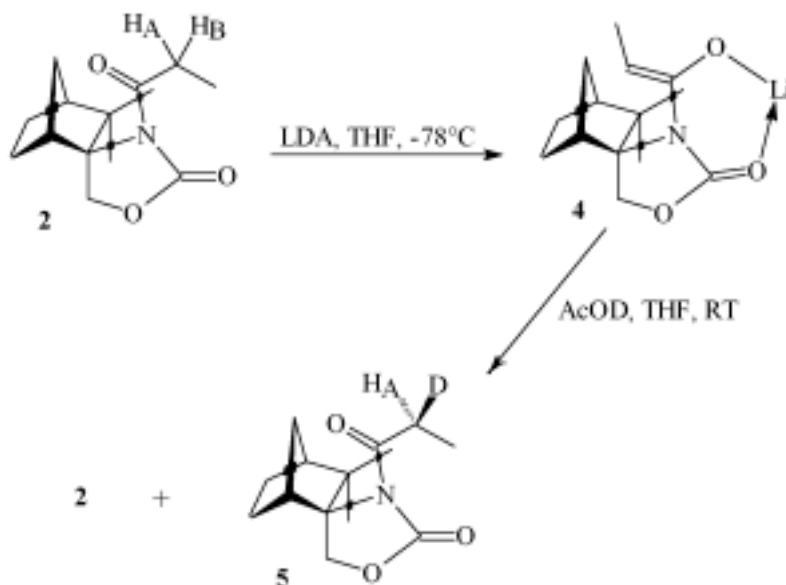
Results and Discussion

Attempts to distinguish between the prochiral methylene protons H_A and H_B in the *N*-propionyl derivative of the chiral auxiliary spiro-oxazolidin-2-one **2** were carried out by using nuclear Overhauser effect (nOe) studies of **2**^[6]. Unfortunately, there is no differential enhancements of the prochiral protons H_A and H_B , *i.e.* the protons are not distinguishable^[6].

To solve this assignment problem, altering of the *N*-propionyl derivative **2** by chemical methods, but not too radically, was used as an aid to analyse and discriminate between the prochiral methylene protons H_A and H_B . Specific deuteration, either by synthesis or by H, D exchange, is one of the many possibilities that exist for chemically altering a molecule.

All nuclides that have a spin greater than half, such as ^2H , ^6Li and ^{14}N , have an electric quadrupole moment eQ , and they usually give broad NMR signals due to the shortening of the relaxation times through the interaction of the quadrupole moment with local electric field gradients^[7]. Often this means that one is unable to observe any multiplet splittings due to couplings with other nuclei, or even to resolve chemical shift difference. Exceptions to this are those nuclides that have a relatively small quadrupole moment, such as deuterium. The hydrogen isotope deuterium plays an important indirect role in ^1H NMR spectroscopy. Deuteration or replacement of some of the protons in the molecule by ^2H simplifies the spectrum of the remaining protons.

In order to distinguish between the prochiral methylene protons H_A and H_B in the *N*-propionyl derivative of the chiral auxiliary spiro-oxazolidin-2-one **2**, the partial deuteration of one of these two prochiral methylene protons was employed. A new method was performed for this purpose. Thus, the *N*-propionyl derivative **2** was added to a freshly generated solution of lithium di-isopropyl amide (LDA) at -78°C in anhydrous THF to form the lithium enolate **4**. The acetic acid-*d* AcOD ($\text{CH}_3\text{CO}_2\text{D}$), which was prepared by adding deuterated water to acetic anhydride, was then added to the enolate to yield non-isolated mixture of both the *N*-propionyl derivative **2** and its partially deuterated derivative **5** (Scheme 2).



SCHEME 2

^1H NMR spectrum of expanded region (δ 2.6-3.1 ppm) for the *N*-propionyl derivative **2** is illustrated in Fig. 1 and in particular shows a doublet of quartets for H_A centered at δ 2.99 ppm and another doublet of quartets for H_B at δ 2.80 ppm. Typically the ^1H NMR spectrum of prochiral methylene protons H_A and H_B of the *N*-propionyl derivative **2** is expected to show four lines indicative of an AB spin system. Each of the four lines of the AB system in the *N*-propionyl derivative is further split into a quartet by coupling of the diastereotopic protons H_A and H_B with the vicinal methyl protons. This effect affords the coupling patterns of the prochiral methylene protons H_A and H_B ; *viz* a doublet of quartets for each proton. The coupling constants $J_{H_A H_B}$ and $J_{H_A-H_B/\text{Me}}$ were calculated and found to be 17.6 and 7.3 Hz, respectively.

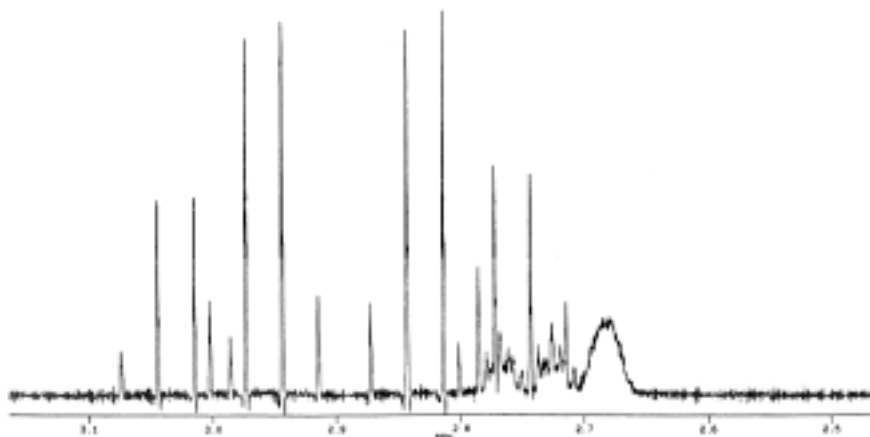


FIG. 1. A portion of the 400 MHz ^1H NMR spectrum of the *N*-propionyl derivative **2**.

By comparison, ^1H NMR spectrum of expanded region (δ 2.6-3.1 ppm) for the partially deuterated product is illustrated in Fig. 2 which shows a doublet of quartets for H_A at δ 2.99 ppm and another doublet of quartets for H_B at δ 2.80 ppm for non-deuterated *N*-propionyl derivative **2**. In the main time, slightly broad signals of quartet of triplets due to $\text{CH}_\text{A}\text{D}$ signal appear at chemical shift 2.99-2.88 ppm and superimposed on the H_A doublet of quartets signal. The coupling constants $J_{\text{H}_\text{A}\text{D}}$ and $J_{\text{H}_\text{A}\text{D}/\text{Me}}$ were found to be 2.7 and 7.3 Hz, respectively. Whilst, there are no extra signals superimposed on the H_B doublet of quartets signal at δ 2.80 ppm, confirming that there is no $\text{CH}_\text{B}\text{D}$ signal. This result confirms that H_B signal in the partially deuterated derivative **5** was disappeared and this is evidence that H_B is the proton which was deuterated.

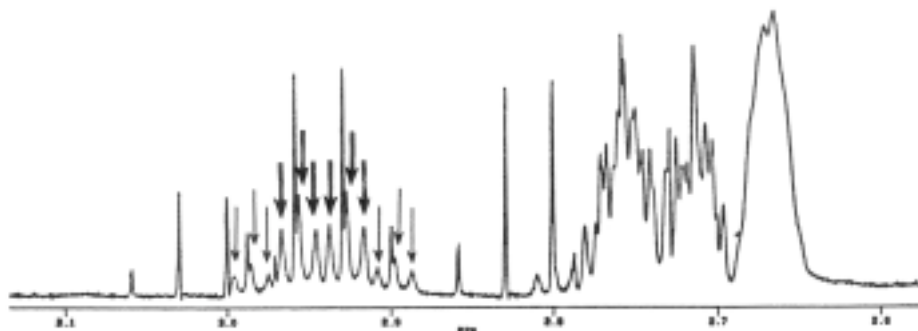


FIG. 2. A portion of the 400 MHz ^1H NMR spectrum of the non-isolated mixture of the *N*-propionyl derivative **2** and its partially deuterated derivative **5**.

The ^1H NMR spectrum of $\text{CH}_\text{A}\text{D}$ signal shows quartet of triplets (Fig. 2). To explain splitting pattern of $\text{CH}_\text{A}\text{D}$ signal, firstly, $\text{CH}_\text{A}\text{D}$ signal is split into a

quartet by coupling of proton H_A with the vicinal methyl protons. Secondly, each line of the quartet splits into a triplet by coupling of proton H_A with the geminal deuterium, which was substituted instead of H_B . The inner lines of the quartet split into stronger triplets than the outer lines (thick arrows point to the inner triplets, whereas, thin arrows point to the outer triplets).

The amount of coupling that takes place between hydrogen and deuterium, J_{HD} , can be measured easily. From theory and empirical data^[8], it is known that the ratio of two coupling constants J_{HH} and J_{HD} is given by the ratio of the gyromagnetic ratios of the two nuclei, and thus we have the relationship: $J_{HH} / J_{HD} = \gamma_H / \gamma_D = 6.51$. This relationship can be used to calculate either of the coupling constants (J_{HH} and J_{HD}) from the other, and it was used to calculate J_{HAHB} in the *N*-propionyl derivative **2** and found to be 17.6 Hz ($J_{HAHB} = J_{HAD} \times 6.51 = 2.7 \times 6.51 = 17.6$ Hz). This relationship confirms that magnitude of J_{HAHB} in the *N*-propionyl derivative **2** which calculated and obtained by other relationship^[9] ($J_{HAHB} = ((C1-C2) + (C3-C4))/2$) Hz, *i.e.* C1, C2, C3 and C4 are centers of AB system) is definitely true.

Thus, deuteration occurs exclusively at only one of the diastereotopic methylene proton sites. Attack by D^+ on intermediate and takes place by the sterically least hindered path *i.e.* remote from the camphene moiety. The deuterium atom thus occupies the site shown in compound **5**.

In conclusion, selective deuteration has allowed unambiguous assignment of the diastereotopic methylene protons H_A and H_B .

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تحضير ودراسات $^1\text{H NMR}$ الطيفية لمشتق N -بروبيونايل
المستبدل جزئيا بالديوتيريوم لمركب كيرالي مساعد Chiracamphox
سبيرو-أوكسازوليدين-٢-ون

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المستخلص . من أجل التمييز بين بروتوني البروكيرال ميثيلين H_B و H_A في مشتق N -بروبيونايل للمركب الكيرالي المساعد سبيرو-أوكسازوليدين-٢-ون تم توظيف طريقة الاستبدال الجزئي لأحد هذين البروتونين بالديوتيريوم . طريقة جديدة استخدمت لتحضير مشتق N -بروبيونايل المستبدل جزئيا بالديوتيريوم بواسطة ليثيوم ثنائي -إيزوبروبايل أميد (LDA) لعمل إنوليت الليثيوم الذي تمت معالجته بواسطة AcOD ليتج خليط غير مفصول من مشتق N -بروبيونايل ومشتقه المستبدل جزئيا بالديوتيريوم . دراسات $^1\text{H NMR}$ للنتائج أظهرت أن الاستبدال الجزئي بالديوتيريوم قد تم فعلا . وأثبتت أن البروتونين الدياستيريوميريان H_B و H_A يمكن التمييز بينهما .