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SYNTHESIS AND NOE AND 2D-NOESY SPECTROSCOPIC STUDIES OF TWO *N*-PROPIONYL DERIVATIVES OF TERPENE-DERIVED CHIRAL AUXILIARIES

Tariq R. Sobahi
Department of Chemistry, Faculty of Science, King Abdulaziz University,
Jeddah-21413, P.O.Box 9028, Saudi Arabia
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تحضير مشتقين N–بروبيونايل من المركبات الكيرالية المساعدة المشتقة من التربينات (أحدهما مشتق من (–)–٣–بينانول، والآخر مشتق من أيزومنثول) تم إنجازها بواسطة استعمال بيوتايل ليثيوم عادي كقاعدة و بروبيونايل كلورايد ككاشف للأسيلة. من أجل زيادة محصلة النواتج لكلٍ من مشتقي N–بروبيونايل خاصةً المشتق من أيزومنثول، تم استخدام كاشف أسيلة آخر لهذا الغرض. استخدام كاشف الأسيلة (الرخيص والمتوفر تجارياً) بروبيونيك أنهيدريد أعطى تقريباً نفس الحصيلة لمشتق N–بروبيونايل المشتق من (–)–٣–بينانول، لكن لسوء الحظ هذه الطريقة لم ترفع الحصيلة لمشتق N–بروبيونايل المشتق من أيزومنثول كثيراً على الرغم من ارتفاعها قليلاً. المحاولات للتمييز بين بروتون البروكيرال ميثيلين في مجموعة N–بروبيونايل وجميع البروتونات ومجموعات الميثايل الدياستيريوميرية الأخرى في مشتقي N–بروبيونايل للمركبات الكيرالية المساعدة قد تم أداؤها باستخدام أطياف nOe المطروحة لرنين البروتون النووي المغناطيسي وكذلك باستخدام دراسات 2D-NOESY الطيفية.

The synthesis of two *N*-propionyl derivatives of terpene-derived chiral auxiliaries (one is derived from (-)-3-pinanol, and the other from isomenthol) has been achieved *via* the use of *n*-butyllithium as a base and propionyl chloride as an acylation reagent. In order to increase the yield of both *N*-propionyl derivatives, particularly *N*-propionyl derivative of chiral auxiliary derived from isomenthol, the alternative acylation reagent was employed for this purpose. Using, cheap and readily available acylation reagent, propionic anhydride gave almost the same yield of *N*-propionyl derivative of chiral auxiliary derived from (-)-3-pinanol, but unfortunately, this procedure did not increase the yield of the *N*-propionyl derivative of chiral auxiliary derived from isomenthol much, although it was slightly better. Attempts to distinguish between the prochiral methylene protons in the *N*-propionyl group, and all other diastereotopic protons and methyl groups in these two *N*-propionyl derivatives of chiral auxiliaries were carried out by using ^{1}H NMR nOe difference spectra and 2D-NOESY spectroscopic studies.

INTRODUCTION

The synthetic route chosen for the synthesis of the chiral oxazolidinone auxiliaries used as starting materials, cheap readily available chiral alcohol and involved a stereospecific intra-molecular nitrene insertion process [1]. This nitrene insertion route to chiral oxazolidinones has been used previously by Paryzek [2] and Alewood [3] in the field of steroid chemistry. The chiral substrates selected for investigation were terpene alcohols which are available from the chiral pool. The first one to be investigated was (-)-3-pinanol **1** which was chosen and used by Cadogan *et al* [4,5] as the starting material for the synthesis of the chiral oxazolidinone auxiliary **4** (Scheme 1). Azidoformate **3** was synthesized from **1** according to the sequence shown in Scheme 1. This azidoformate **3**, which was an oil, was thermally decomposed using flash vacuum pyrolysis (300°C, 0.02mmHg). This produced a mixture consisting of the oxazolidinones **4** and **5** in the ratio of 3:1 respectively. The major product **4** was easily isolated by flash column chromatography in a yield of 65% [4,5].

EXPERIMENTAL

Preparation of (2*R*,6*S*) - 3 -aza-2,9,9-trimethyl-5-oxatricyclo[6.1.1.0^{2,6}]decan-4-one (4) and (1*S*,4*R*,6*S*)-9-aza-1-isopropyl-4-methyl-7-oxabicyclo[4.3.0]nonane-8-one (9).

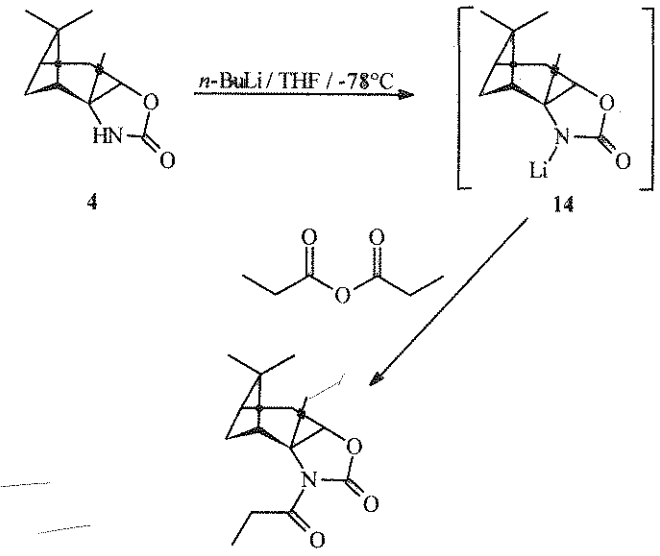
Literature methods were used to prepare (2*R*,6*S*)-3-aza-2,9,9-trimethyl-5-oxatricyclo[6.1.1.0^{2,6}]-decan-4-one (**4**) [4,5] and (1*S*,4*R*,6*S*)-9-aza-1-isopropyl-4-methyl-7-oxabicyclo[4.3.0]nonane-8-one (**9**) [4,5].

Preparation of (2*R*,6*S*)-*N*-propionyl-3-aza-2,9,9-trimethyl-5-oxatricyclo[6.1.1.0^{2,6}]decan-4-one (12).

To a solution of *auxiliary* **4** (0.50 g, 2.56 mmol) in dry THF (20ml), at –78 °C under argon, was added *n*-butyllithium (1.76ml of 1.6M solution, 2.82 mmol, 1.1 eq) *via* syringe. After stirring for 30 minutes a solution of freshly distilled propionic anhydride (0.521g, 4.00mmol, 1.56 eq) in THF (5ml) was added dropwise *via* syringe. The resulting solution was stirred at –78 °C for 5 minutes before being allowed to warm to room temperature and then stirred at this temperature for 30 minutes. TLC analysis revealed that the reaction was complete and quenching was effected with sodium carbonate solution. After stirring for 10 minutes at room temperature, the layers were separated and the aqueous layer extracted with dichloromethane (3x20ml). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over ($MgSO_4$), filtered and evaporated to yield a pale yellow oil which was purified by flash chromatography (50g silica) using *n*-hexane:ether (4:1) as elution solvent to give **(12)** as a colourless solid which was recrystallised from hexane to give the pure compound as a colourless crystals (0.527g, 82%); mp 101-102°C (from hexane); FTIR (nujol) ν_{max} 1770(oxazolidinone C=O), 1700(C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (1H, dd, *J*=8.9, 2.6 Hz, CH_NO), 2.95 (1H, dq, *J*=17.9, 7.23 Hz, CH_MH_KC=O), 2.90 (1H, dq, *J*=17.9, 7.23 Hz, CH_MH_KC=O), 2.92 (1H, dd, *J*= 4.7 Hz, H_L), 2.52-2.40 (1H, m, CH_J), 2.33-2.23 (1H, m, H_H), 2.01-1.99 (1H, m, CH_G), 1.98-1.92 (1H, m, H_F), 1.66 (3H ,s ,$CH_{3\ (E)}$), 1.31 (3H ,s ,$CH_{3\ (D)}$), 1.11 (3H, t, *J*=7.3 Hz, $CH_{3(C)}CH_2$), 1.02 (1H, d, *J*=11.2 Hz, H_B), 0.93 (3H, s, $CH_{3\ (A)}$) ppm; ^{13}C NMR (100.2 MHz, CDCl3) δ 174.69 (C=O), 153.90 (C=0), 76.46(CHO), 67.56(quatC), 46.16(CH_L), 38.84 (CH_G), 37.97(quatC), 34.79(CH_JH_F), 30.61 (CH_MH_K), 27.35(CH_HH_B, $CH_{3\ (D)}$), 25.58 ($CH_{3\ (E)}$), 24.26($CH_{3\ (A)}$), 8.43($CH_{3\ (C)}$) ppm; MS (EI) m/z 32(63%), 41(34), 57(base), 109(38), 251(71,M^+); Accurate mass (EI); Found: 251.15213 (85%); $C_{14}H_{21}NO_3$ (M^+) requires 251.15213.

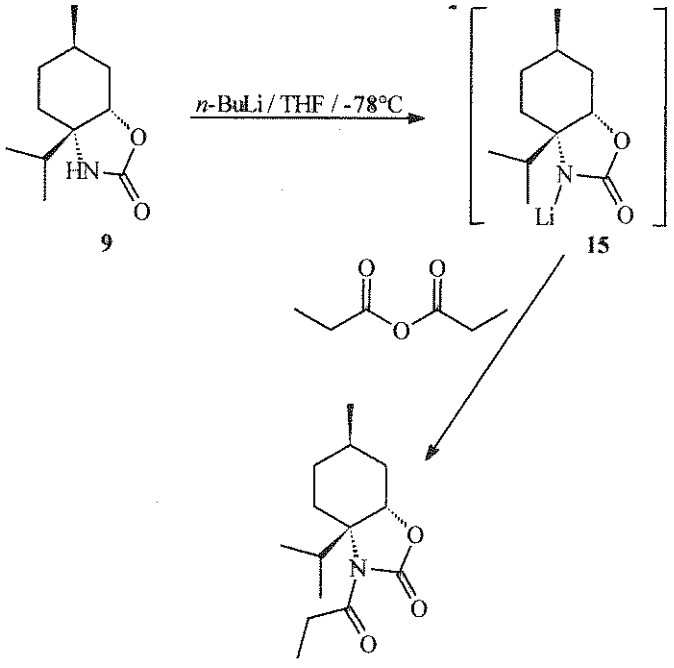
Preparation of (1*S*,4*R*,6*S*)-*N*-propionyl-9-aza-1-isopropyl-4-methyl-7-oxabicyclo[4.3.0] nonane-8-one 13.

A similar procedure to that for the preparation of **12** was adopted for the *N*-propionyl derivative of *auxiliary* **9** although the combined organic extracts were washed with water (20ml), dried ($MgSO_4$), filtered and evaporated to yield a slightly pale yellow viscous oil. The residue was subjected to flash column chromatography (50g silica) using hexane:ether (1:1) elution to give **13** as clear oil which crystallized on standing (0.322g, 50%); mp 51.9-53.2 °C; FTIR (nujol) ν_{max} 1762(oxazolidinone C=O), 1712(C=O) cm^{-1}; ^{1}H NMR (400 MHz , $CDCl_3$) δ 4.44 (1H, t, *J*=2.8 Hz, CH_QO), 2.98 (1H, dq, *J*=17.7, 7.3 Hz, $CH_PH_NCH_3$), 2.92 (1H, dq, *J*=17.7, 7.3 Hz, $CH_PH_NCH_3$), 2.72 (1H, septet, *J*=6.9 Hz, CH_M),



4 14 12

Sceheme 3



9 15 13

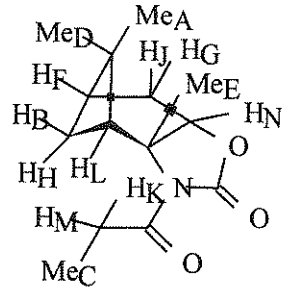
Sceheme 4

13.6% and 8.3 % enhancement of signal, respectively, due to H_K, but did not cause enhancement of signal for H_M. All of these results prove that discrimination between the diastereotopic protons H_K and H_M was achieved by irradiation of H_J, H_D and H_E, individually.

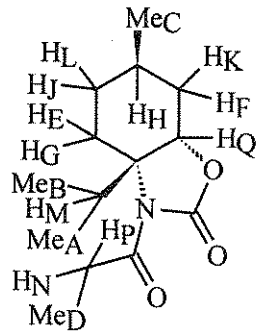
Fig. 1 illustrates a portion of the 2D-NOESY spectrum of the *N*-propionyl derivative **12**. The one-dimensional spectrum, as with COSY, is found along the diagonal, and cross peaks occur when two protons are close in space. Thus, methyl D protons and methyl E protons show two cross peaks with proton H_K at δ 2.90 and 1.31 and at 2.90 and 1.66 ppm, respectively. That proves H_K is in close in space to two methyl protons H_D and H_E. There is another cross peak at δ 2.92 and 2.29 ppm, confirming that H_K and the bridgehead proton H_L are both close in space to H_H. All of these results determined by NOESY spectrum confirm all results determined by nOe difference spectra and all of them confirm that H_K and H_M are distinguishable.

Table 2 shows that irradiation of methyl A protons, methyl B protons, methyl C protons, methyl D protons, H_E, H_F, H_G and H_H, individually, gave 21%, 20.7%, 21.1%, 20.7%, 18.2%, 17.8%, 12.0% and 21.1% enhancement of signal, respectively, for H_L, whereas, all of these irradiations did not affect H_J. Irradiation of H_Q only gave 2.9% enhancement of signal for H_J. These results confirm that H_L is close in space to H_A, H_B, H_C, H_D, H_E, H_F, H_G and H_H, whilst, H_J is close in space to H_Q. These results prove that discrimination between the diastereotopic protons H_J and H_L was achieved by irradiation of protons H_A to H_H or irradiation of H_Q.

Irradiation of H_G and H_H, individually caused 12.4% and 3.3% enhancement of the signal, respectively, due to H_F, whereas, irradiation of these protons did not affect H_K. That proves H_F is close in position to H_G and H_H. Irradiation of H_J, H_p and H_Q, individually, caused 3.7%, 2.9% and 2.9% enhancement of the signal, respectively, due to H_K, but did not affect HF. That proves H_K is close in position to H_J, H_p and H_Q. These results confirm that diastereotopic methylene protons H_F and H_K are distinguishable.



12



13

Irradiation of methyl D protons, H_F, H_J, H_K, H_L, H_M, H_N, H_P and H_Q, individually, gave 6.6%, 5.4%, 20.7%, 13.2%, 20.7%, 20.7%, 18.2%, 20.7% and 24.8% of enhancement of signal, respectively, for H_G, whilst, did not affect on H_E. That proves H_G is close in space to all of these protons. Irradiation of H_H gave 2.1% enhancement of signal for H_E, but did not affect H_G. These results prove that discrimination between the diastereotopic protons H_E and H_G was achieved by irradiation of H_D, H_F, H_J, H_K, H_L, H_M, H_N, H_P and H_Q, individually, or irradiation of H_H.

Discrimination between the two diastereotopic methyl groups A and B was achieved by irradiation of H_H which gave 4.6% enhancement of signal for H_B, but did not affect on H_H, whereas, irradiation of H_G and H_Q gave 4.5% and 3.7% enhancement of signal, respectively, for H_A, and 6.2% and 2.1% enhancement of signal, respectively, for H_B. These results prove that H_B is close in space to H_H, and it is closer to H_G than H_A, but H_A is closer in space to H_Q than H_B.

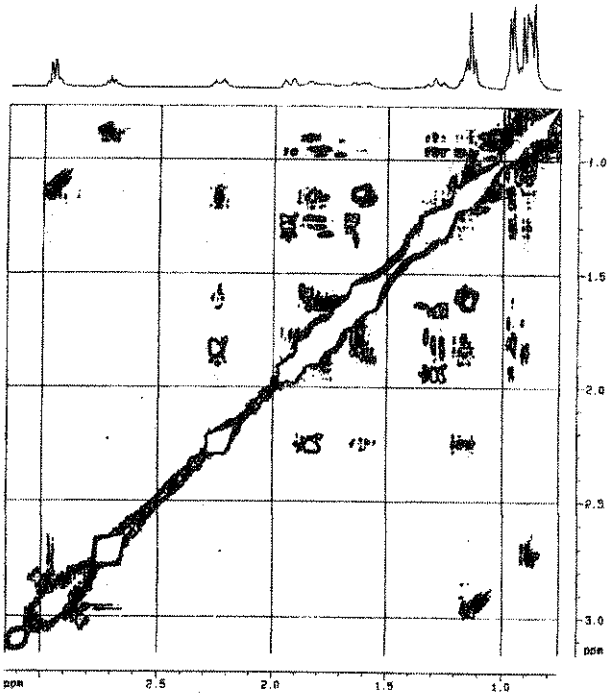


Fig. 2: A portion of the 2D-NOESY 400 MHz NMR spectrum of the *N*-propionyl derivative 13

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