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(5*R*)-5-Alkyl-5,6-dihydroindolizines via stereospecific domino hydroformylation/cyclodehydration of (3*R*)-3-(pyrrol-1-yl)alk-1-enes

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Abstract—(5*R*)-5-Alkyl-5,6-dihydroindolizines **3a**–**c** having the same high enantiomeric excess (>92%) as the corresponding starting olefins (3*R*)-3-(pyrrol-1-yl)alk-1-enes **1a**–**c** were obtained via a highly regioselective and stereospecific domino hydroformylation/cyclodehydration reaction sequence. The reasons for this configurational stability were also analyzed in the light of the general accepted rhodium catalyzed hydroformylation mechanism.

1. Introduction

The construction of pyrrole fused alkaloids of the 'izine' or 'izidine' types in a stereoselective manner is a topic of current interest due to the wide ranging biological activity associated with these systems. Among the many synthetic approaches, the oxo process is still poorly investigated. Nevertheless the hydroformylation of olefins presents many attractive features: the reaction needs only catalytic amounts of a metal catalyst and all atoms of the starting materials remain incorporated into the product in a very economic C–C-bond forming reaction. When the oxo process is a part of a domino reaction sequence and involves optically active species, its potential is greatly enhanced.[1] A critical aspect could still be the control of the regio and enantioselectivity of the reaction depending on unsymmetrically substituted and/or configurationally unstable olefins as starting material. Recently we set up a new synthetic application of the oxo process giving 5-alkyl-5,6-dihydroindolizines from 3-(pyrrol-1-yl)alk-1-enes via in situ cyclodehydration of the thus formed linear 4-pyrrolylbutanals.[2] On the contrary the branched aldehyde, present in minor amounts, did not undergo the same reaction, remaining unchanged at the end of the reaction.

2. Results and discussion

Encouraged by the above successful application and taking into account that optically active 5-alkyl-5,6-dihydroindolizines could be precursors of natural indolizidines,[3] we planned to hydroformylate the highly enantiomerically enriched (3*R*)-3-(pyrrol-1-yl)alk-1-enes **1a**–**c**, recently synthesized by us:[4] the (5*R*)-5-alkylindolizidines **3a**–**c** having the same enantiomeric excess (>92%) as the starting olefins were obtained via a highly regioselective and stereospecific domino transformation (Scheme 1, Table 1).

The (3*R*)-3-(pyrrol-1yl)alk-1-enes **1a**–**c** (ee >92%) were prepared via a multistep reaction sequence using D-α-aminoacids as the source of chirality.[4] The hydroformylation of the substrates **1a**–**c** was carried out in the presence of $Rh_4(CO)_{12}$ as the catalyst precursor according to a typical procedure.[5] Under these conditions the formed linear aldehydes **2** undergo an in situ intramolecular electrophilic substitution on position two of the pyrrole nucleus giving 5,6-dihydroindolizines **3** via formation of a bicyclic alcohol followed by

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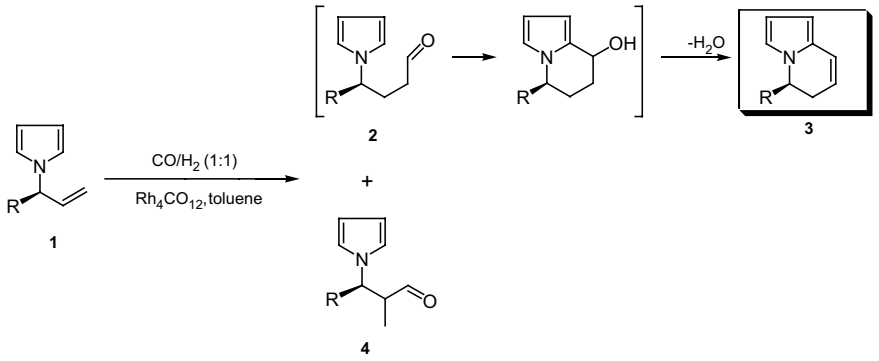


Scheme 1. Hydroformylation of (3*R*)-3-(pyrrol-1-yl)alk-1-enes **1a**–**c** in the presence of $Rh_4(CO)_{12}$ at 100 °C and 125 °C.

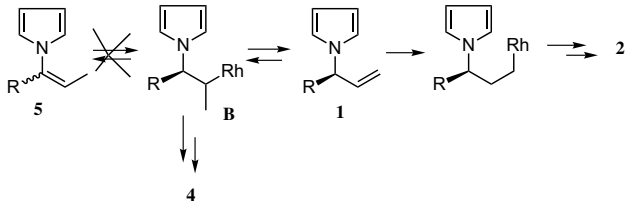
Table 1. Hydroformylation of (3*R*)-3-(pyrrol-1-yl)alk-1-enes **1a**–**c** with $Rh_4(CO)_{12}$ at 100 °C

1		*T* (°C)	*P* (atm)	Reaction time (h)	Conversion (%)	Products		
Entry	Ee (%)[a]					**3/4** (%)	**3** Yield (%)[b]	**3** Ee (%)[a]
a	98	100	100	0.2	25	57/43	—	98
a	98	100	100	1.5	99	59/41	55	98
a	98	125	30	0.5	97	85/15	73	98
b	92	125	30	0.5	99	87/13	70	92
c	92	125	30	0.5	99	84/16	75	92

a: R = Me; **b**: R = *iso*-Pr; **c**: R = *n*-Pr.
[a] Determined by gas chromatography with the chiral capillary column CHIRALDEX G-TA (γ-cyclodextrin trifluoroacetyl, 50 m × 0.25 mm).
[b] Isolated pure product.

dehydration (Scheme 1). Compound **1a** was submitted under the same experimental hydroformylation conditions adopted for the corresponding racemic substrate,[2c] showing a very similar behaviour. After 0.2 h the conversion was 25% and the reaction mixture comprised 5-methyl-5,6-dihydroindolizine **3a** and branched aldehyde **4a** in a 57/43 molar ratio. This value remained unchanged at total conversion (after 1.5 h, 59/41 regioisomeric ratio) (Table 1). The linear aldehyde **2a**, the precursor of **3a**, was present only in trace amounts in the reaction mixture both at partial and complete substrate conversion, the cyclization reaction being faster than hydroformylation. An evaluation of the enantiomeric excess of both unconverted **1a** and produced **3a** was carried out in order to test the configurational stability of these structures under hydroformylation conditions. Interestingly **1a** showed, at all conversions, practically the same ee, that is, the starting ee value (98%). A similar behaviour occurred for the dihydroindolizine **3a**, its ee value remaining the same as the corresponding olefin **1a** (98%) at all reaction times (Table 1). Encouraged by this result, we turned our attention to setting up hydroformylation conditions able to increase the formation of optically active 5-methyl-5,6-dihydroindolizine, that is, directing the regioselectivity towards the linear aldehyde. According to the well documented behaviour of vinyl and allyl substrates under rhodium-catalyzed hydroformylation,[2a,6] a marked improvement was achieved by carrying out the hydroformylation of **1a** at 125 °C and at lower pressure (30 atm; $CO/H_2 = 1:1$): the molar ratio **3a/4a** conveniently increased to 85/15. It is to note that these forcing conditions do not affect the enantiomeric excess of **3a** (ee 98%). The other olefins **1b**–**c** were submitted to the same hydroformylation conditions. In particular the olefin **1b** gave 5-*i*-propyl-5,6-dihydroindolizine **3b** in **3b/4b**[7] = 87/13 regioisomeric ratio. In a similar manner 5-*n*-propyl-5,6-dihydroindolizine **3c** was obtained from **1c** (**3c/4c**[7] = 84/16). No traces of the linear aldehydes **2b** and **c**, the precursors to **3b** and **c**, were observed in the reaction mixture both at partial and complete substrate conversion. The dihydroindolizines **3b** and **c**[8] are new compounds and were isolated and characterized by ^1H and ^{13}C NMR spectroscopy, GC–MS and specific rotation. The racemic dihydroindolizine **3a** is known[9] while its optically active form has been prepared here for the first time. All the obtained dihydroindolizines are stable enough to be handled easily at room temperature without any decomposition or change of enantiomeric excess and can be stored at 0 °C for long periods. The ee values of the isolated 5,6-dihydroindolizines were determined by gas chromatography with a chiral capillary column. The chromatographic conditions were tested on the analogous racemic substrates obtained via the same oxo process starting from racemic olefins. In particular **1b** and **c** were prepared via the multistep synthetic pathway adopted for the corresponding optically active substrates,[4] starting from the appropriate racemic amino acids. Compound **1a** was easily prepared via *N*-alkylation of pyrrole with 3-chloro-1-butene under basic conditions.[2c]

The very high ee values obtained for **3** indicate that the hydroformylation conditions are perfectly compatible with the optically active pyrrolylolefins employed allowing a complete configurational stability also under potentially isomerizing conditions (high temperature and low pressure). Taking into account the general



Scheme 2.

accepted mechanism of hydroformylation,[10] we can affirm that, under the above conditions, the branched alkyl-rhodium intermediate **B** undergoes a β-hydride elimination process[2c] not involving the stereogenic centre, generating the olefin **1** again and not **5** (Scheme 2).

In fact no traces of the internal olefin **5** were observed in the crude reaction mixture at both partial or total conversion. Due to the influence of the electron withdrawing heteroaromatic effect, the methinic hydrogen bonded to the carbon vicinal to the annular nitrogen into **B** probably does not have sufficient hydride character for β-hydride elimination.

3. Conclusion

In conclusion, the chemistry reported here is a synthetic application of the rhodium-catalyzed hydroformylation providing new optically active 5-alkyl-5,6-dihydroindolizines. Suitable experimental conditions avoiding racemization and enhancing the regioselectivity were set up making the protocol a general regioselective and stereospecific method for optically active 5-alkyl-5,6-dihydroindolizines. Investigations into diastereoselective and stereospecific hydrogenation of the obtained dihydroindolizines to 5-alkyloctahydroindolizines of natural origin are in progress.

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7. **4b**: MS *m/e* 179 (M^+ 30), 161 (52), 151 (38), 136 (37), 122 (57), 108 (85), 95 (63), 80 (43), 68 (100). **4c**: MS *m/e* 179 (M^+ 8), 151 (30), 122 (36), 108 (28), 95 (12), 80 (36), 68 (100).
8. For **3a** $[\alpha]_D^{26} = -107.5$ (*c* 1.18, CH_2Cl_2). Selected data for **3b**: as a orange oil (SiO_2, CH_2Cl_2/hexane = 1/7) 70% yield. $[\alpha]_D^{26} = -60.8$ (*c* 1.08, CH_2Cl_2). ^1H NMR: δ 6.66 (t, $J = 2.2$ Hz, 1H), 6.41 (dd, $J = 2.3$; 9.6 Hz, 1H), 6.12 (dd, $J = 2.8$; 3.4 Hz, 1H), 6.03 (dd, $J = 1.5$; 3.7 Hz, 1H), 5.64 (m, 1H), 3.84 (m, 1H), 2.65 (m, 1H), 2.44 (m, 1H), 2.22 (m, 1H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.86 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR δ 18.51, 19.4, 25.8, 31.4, 60.0, 105.5, 106.8, 117.9, 119.8, 121.0, 128.9. MS *m/e* 161 (M^+ 80), 146 (3), 132 (2), 118 (100), 91 (22), 63 (5), 39 (10). Selected data for **3c**: as a orange oil (SiO_2, CH_2Cl_2/hexane = 1/7) 75% yield. $[\alpha]_D^{26} = -43.5$ (*c* 0.86, CH_2Cl_2) ^1H NMR: δ 6.68 (t, $J = 1.8$ Hz, 1H), 6.42 (d, $J = 9.8$ Hz, 1H), 6.13 (t, $J = 3.1$ Hz, 1H), 6.03 (b s, 1H), 5.63 (m, 1H), 4.04 (q, $J = 6.5$ Hz, 1H), 2.68 (m, 1H), 2.28 (m, 1H), 1.85–1.25 (m, 4H), 0.95 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR: δ 13.6, 18.9, 28.9, 36.2, 53.8, 105.6, 107.1, 117.2, 119.3, 119.6, 127.9. MS *m/e* 161 (M^+ 40), 132 (6), 118 (100), 91 (8).
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