Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 497–499

TETRAHEDRON: *ASYMMETRY*

Asymmetric catalysis. Part 137: Nickel catalysed enantioselective α-ketol rearrangement of 1-benzoylcycloalkanols†

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Received 15 January 2001; accepted 24 January 2001

Abstract—Using catalytic amounts of Ni complexes the tertiary α-hydroxyketones 1-benzoylcyclobutanol **1** and 1-benzoylcyclopentanol **3** undergo α-ketol rearrangement. The use of the chiral ligand 2,6-bis[(4*S*)-isopropyl-2-oxazolin-2-yl]pyridine gave an enantiomeric excess of about 34% for both systems, forming (−)-2-hydroxy-2-phenylcyclopentanone **2** and (*R*)-(−)-2-hydroxy-2-phenylcyclohexanone **4**. 1-Benzoylcyclohexanol **5** could not be catalytically rearranged to **6** under these conditions.

1. Introduction

In the rearrangement of α-hydroxyketones, shown in Scheme 1, the carbon skeleton isomerises via migration of its alkyl or aryl substituents. Reactions of this type have recently been investigated using achiral compounds of the type **a** as substrates and homochiral catalysts to lead to the preferred formation of one or the other enantiomer **b** or **c** of the product.[2]

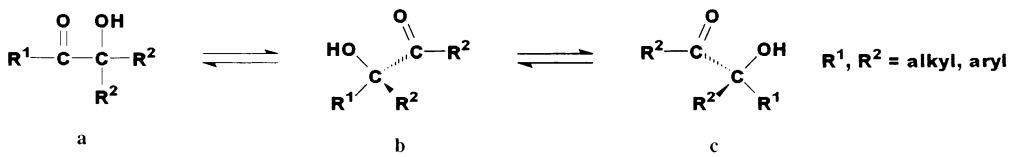
The rearrangement is a reversible reaction, and in the first step one of the substituents R^2 in **a** migrates from the hydroxy carbon atom to the carbonyl carbon atom. A proton shift completes the role change of the carbonyl and the hydroxy function. Subsequently, R^1 may also take part in the rearrangement. Therefore, in order to achieve enantiocontrol, the reaction has to be stopped before equilibrium is reached and, as such, a compromise between high enantioselectivity and conversion has to be found.

Ideally, the first step of the rearrangement should be much faster than the subsequent reaction steps. Strained ring systems should therefore be perfect starting materials as the ring enlargement should be fast and complete, and the back reaction should not occur. Possible candidates fulfilling these demands are the 1-benzoylcycloalkanols 1-benzoylcyclobutanol **1** and 1-benzoylcyclopentanol **3** (Scheme 2).

2. Results and discussion

The Ni catalysts chosen for the rearrangement of the cyclic α-ketols **1** and **3** were similar to those established for the isomerisation of the linear α-ketols 2-hydroxy-2-methyl-1-phenylpropan-1-one and 2-hydroxy-2-methylpentan-3-one[2] and the epimerisation of aldoses.[3]

Reaction temperatures and times were investigated in an attempt to optimise the reactions.[4] Initially, 1-ben-



a b c

Scheme 1. α-Ketol rearrangement.

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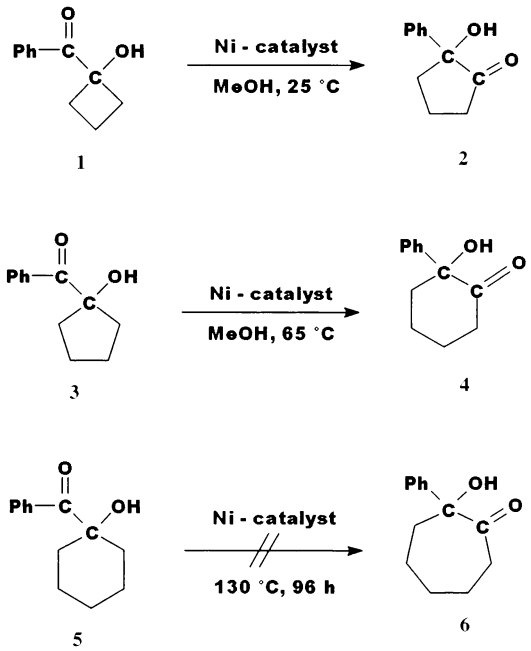
† For Part 136, see: Ref. 1.

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00045-3



Scheme 2. α-Ketol rearrangement of 1-benzoylcyclobutanol **1**, 1-benzoylcyclopentanol **3** and attempted rearrangement of 1-benzoylcyclohexanol **5**.

zoylcyclobutanol **1** was isomerised in the presence of 2 mol% of the achiral $NiCl_2$/TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) catalyst system in a molar ratio of 1:2. The reaction was carried out in methanol and the rearrangement was complete after 6 h at 25°C.

$NiCl_2$/2,6-bis[(4*S*)-isopropyl-2-oxazolin-2-yl]pyridine ($NiCl_2$/pybox) was then tested as a chiral catalyst under similar conditions and the reaction was complete after 4 h. In two parallel experiments, an enantiomeric excess (e.e.) of 33.6 and 27.3% of (−)-2-hydroxy-2-phenylcyclopentanone (absolute configuration unknown) was obtained. The e.e. of (−)-2-hydroxy-2-phenylcyclopentanone was unchanged when the reaction time was extended to 12 h. Repeating the experiments at lower temperatures resulted in a decrease in e.e. to 16.8 and 17.0% at 0°C over 36 h. E.e.s of 7.3 and 7.5% were obtained when the reaction was completed at −25°C over 240 h, whilst completing the reaction at 65°C with a reaction time of 1 h, the e.e.s obtained in parallel experiments were 29.9 and 30.2%.

As the cyclopentane ring of **3** is less strained than its cyclobutane analogue, a higher reaction temperature of 65°C and extended reaction times were necessary for cyclopentanol rearrangement. Using the catalyst system $Ni(acac)_2$/pybox, (*R*)-(−)-2-hydroxy-2-phenylcyclohexanone (assignment of absolute configuration according to Ref. 5) was formed with 91% conversion and an e.e. of 34.2% after 120 h. Further experiments confirmed that, in contrast to the four-membered ring system **1**, a quantitative conversion of **3** to **4** could not be obtained. About 4% of the starting material **3** remained. Similarly, when the rearrangement was carried out in the presence of 0.5 mol/L sodium methoxide under reflux in methanol over 24 h, a 96% conversion was obtained.

Extension of the reaction time to 48 h showed that the **3**:**4** ratio of 4:96 was the equilibrium ratio. The rearrangement of **3** performed at 130°C (no solvent) in the presence of $Ni(acac)_2$/pybox (2 mol%) also gave **4** in 96% yield after 24 h. However, **4** was completely racemised. Consequently, the reaction has to be stopped before equilibration plays a major role to prevent racemisation by the reverse reaction **4** to **3**.[2] Conducting the experiment at 65°C in MeOH in the presence of 2 mol% of pybox only (without the Ni salt), resulted in a drop in both the e.e. to 16.6 and 18.1%, and the conversion to 52%. Additionally, side products, absent in the Ni catalysed reactions, formed in ca. 20% yield.

Attempts to perform the rearrangement of **3** to **4** in solvents other than methanol (toluene, acetonitrile, tetrahydrofuran) at 65°C over 120 h were unsuccessful as the reactions showed only low turnover (<10%) with insignificant enantiocontrol.

Finally, to test the limitations of the procedure, the α-ketol rearrangement of 1-benzoylcyclohexanol **5** was examined. $NiCl_2$/TMEDA 1:2 was used as the catalyst at a loading of 2 mol% in the molten substrate (no solvent). The red colour of the reaction mixture showed that the catalytically active species had formed, however, even after 96 h at 130°C no rearrangement was observed. Obviously, the seven-membered ring system **6** did not form and it is possible that the reaction could take the reverse course, forming **6** from **5**. Currently we are working to extend the scope of this new class of catalytic asymmetric reaction.

3. Experimental

3.1. General remarks

All reactions were performed under an inert atmosphere. All reagents were of the best available commercial grade. Solids were used without further purification, liquids were dried as usual and saturated with nitrogen. The ligand 2,6-bis[(4*S*)-isopropyl-2-oxazolin-2-yl]pyridine was bought from Aldrich®. ^1H NMR spectra were recorded on Bruker AC 250 and ARX 400 instruments. Bulb-to-bulb distillations: Büchi GKR-50.

3.2. 1-Benzoylcyclobutanol 1

1-Benzoylcyclobutanol, **1**, was synthesised according to the literature[6] and used immediately after preparation.

3.3. 2-Hydroxy-2-phenylcyclopentanone 2

A solution of the catalytically active species was prepared by heating $NiCl_2$ (6.5 mg, 0.05 mmol) and ligand (0.1 mmol) in anhydrous MeOH (40 mL) under reflux

for 24 h. The solution was cooled to 25°C, and **1** (440 mg, 2.5 mmol) was added. After stirring at 25°C for 4 h the solvent was removed in vacuo and the sample was purified by bulb-to-bulb distillation. The product was obtained as a colourless oil in quantitative yield (bp 110°C/0.1 hPa). ^{1}H NMR (250 MHz, $CDCl_3$): **1**: $\delta =$ 1.67–1.82 (m, 1H, CH_2), 1.92–2.08 (m, 1H, CH_2), 2.24–2.37 (m, 2H, CH_2), 2.74–2.85 (m, 2H, CH_2), 7.35–7.58 (m, 3H, CH_{arom}), 8.00–8.05 (m, 2H, CH_{arom}). **2**: $\delta =$ 1.70–1.90 (m, 1H, CH_2), 1.95–2.11 (m, 1H, CH_2), 2.13–2.26 (m, 1H, CH_2), 2.35–2.50 (m, 3H, CH_2), 3.33 (s, 1H, OH), 7.32–7.37 (m, 5H, CH_{arom}).

3.4. GC analysis of 1 and 2

Hewlett–Packard 5890 II, split injector (125°C), FID detector (260°C), Spectra-Physics SP 4270 integrator, oven temperature initially 30°C, then heating to 150°C at max. rate, hydrogen as carrier gas, solvent CH_2Cl_2. Baseline separation was obtained using a Rt-βDEX cst column (length 30 m, lumen 0.32 mm, film thickness 0.25 μm). Retention times: 14.5 min (–)-**2**, 15.2 min (+)-**2**, 16.2 min **1**. Assignment of the peaks was based on the optical rotation of enantiomerically enriched samples.

3.5. 1-Benzoylcyclopentanol 3

1-Benzoylcyclopentanol, **3**, was synthesised according to the literature[6] and stored at –40°C.

3.6. 2-Hydroxy-2-phenylcyclohexanone 4

The catalytically active species was prepared as above. After 24 h the substrate **3** (476 mg, 2.5 mmol) was added to the refluxing methanol solution. After stirring under reflux for 120 h the solvent was removed. Bulb-to-bulb distillation gave the product **4** as a colourless oil (A quantitative mass was obtained which was a mixture of **4** (96%) and **3** (4%) as detected by GC analysis). ^{1}H NMR (250 MHz, $CDCl_3$): **3**, $\delta = 1.85$–2.10 (m, 6H, CH_2), 2.30–2.44 (m, 2H, CH_2), 3.75 (s, 1H, OH), 7.30–7.80 (m, 3H, CH_{arom}), 7.90–8.20 (m, 2H, CH_{arom}); **4**, $\delta = 1.63$–1.92 (m, 4H, CH_2), 2.00–2.10 (m, 1H, CH_2), 2.35–2.57 (m, 2H, CH_2), 2.96–3.04 (m, 1H, CH_2), 4.50 (bs, 1H, OH), 7.26–7.43 (m, 5H, CH_{arom}).

3.7. GC analysis of 3/4

Hewlett–Packard 5890 II, split injector (230°C), FID detector (260°C), Spectra-Physics SP 4270 integrator, oven temperature 130°C for 32 min, then heat rate of 8°C/min to 170°C, subsequently 170°C, hydrogen as carrier gas, solvent CH_2Cl_2. Baseline separation was obtained using a Rt-βDEX cst column (length 30 m, lumen 0.32 mm, film thickness 0.25 μm). Retention times: 27.5 min (*R*)-(–)-**4**, 28.8 min (*S*)-(+)-**4**, 37.0 min **3**. Assignment of peaks was based on the optical rotation of enantiomerically enriched samples.

3.8. Enantiomer analysis of 3/4 by ^{1}H NMR

^{1}H NMR analysis using chiral shift reagents confirmed the GC results. This was necessary to exclude thermal rearrangement due to the high oven temperatures. Using trimethylsilylimidazole as a derivatising agent,[7] the trimethylsilyl derivatives both of **3** and **4** were formed. After addition of a four-fold excess of (*S*)-(+)-1-(9′-anthryl)-2,2,2-trifluoroethanol the $OSi(CH_3)_3$ singlet of **4** split and integration was possible. Chemical shifts of the $OSi(CH_3)_3$ protons: $\delta = -0.065$ ppm **3**, –0.079 ppm (*R*)-(–)-**4**, –0.085 ppm (*S*)-(+)-**4**.

3.9. Attempted synthesis of 2-hydroxy-2-phenylcycloheptanone 6

Commercially available 1-benzoylcyclohexanol **5** (2.04 g, 10.0 mmol), $NiCl_2$ (26.0 mg, 0.20 mmol) and TMEDA (46.5 mg, 59.6 μl, 0.40 mmol) were heated to 130°C for 96 h. Bulb-to-bulb distillation (130°C/0.1 hPa) gave the unchanged starting material **5**. ^{1}H NMR (250 MHz, $CDCl_3$): **5**: $\delta = 1.63$–2.05 (m, 10H, CH_2), 7.40–7.57 (m, 3H, CH_{arom}), 7.99–8.03 (m, 2H, CH_{arom}).

Acknowledgements

We thank the DFG and the CNRS for support of our trans-national CERC3 project.

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