Inversion of Configuration of Alcohols with O-Alkyl-N,N'-dicyclohexylisoureas

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(S)-(+)–N,N'-Dicyclohexyl-O-(1-methylheptyl)isourea [(S)-2] reacts with acetic acid in cyclohexane to give (R)-(−)-(1-methylheptyl) acetate [(R)-3] with 100% inversion of configuration. Reaction of isourea (R)-2 with phenol proceeds also with inversion of configuration (99.8%) yielding (S)-(+)–(1-methylheptyl) phenyl ether [(S)-4] as the main product; optically active 2- and 4-(1-methylheptyl)phenols [(S)-5] and [(S)-6], respectively, are formed simultaneously. These byproducts, besides others resulting from hydrate-shifts, document that the mechanism proceeds via the methylheptyl cation intermediate.

O-Alkylisoureas are excellent reagents for alkylations of OH and SH acidic compounds, leading thereby to a series of new synthetic applications. For example, they react smoothly with phenols to form aryl alkyl ethers, and acids are transformed to the corresponding esters in almost quantitative yields. Thiophenols and alkylmercaptans are similarly converted to sulfides. Considering the vast applicability of O-alkylisoureas in the mentioned alkylation reactions, a mechanistic investigation is of considerable interest.

Ever increasing attention has been paid to the use of pure enantiomers as additives, hence enantioselective syntheses of natural products have become very important. The 100% inversion of a chiral centre is gaining in significance.

Starting from O-alkylisoureas of optically active alcohols, the bond breakage occurs at the chiral carbon. We therefore reacted (S)-(+)–2-octanol [(S)-1] with the specific optical rotation [α]D 20 + 10.60° with dicyclohexylcarbodiimide (DCC) in the presence of a small quantity of copper(I) chloride and obtained dextrorotary (S)-N,N'-dicyclohexyl-O-(1-methylheptyl)isourea [(S)-2] in 89% yield. From the reaction of (S)-2 with acetic acid in cyclohexane as solvent, laevorotatory 1-methylheptyl acetate [(R)-3] along with N,N'-dicyclohexylurea (DCU) was isolated (Scheme 1).

Subsequent hydrolysis of (R)-3 with ethanoic sodium hydroxide13 was performed, yielding (R)-(−)-2-octanol [(R)-1] (95%, [α]D 20 - 10.60°, Table 1).

Comparison of the specific optical rotations reveals that only a scant measure of racemization (0.4%) has occurred (with an allowed systematic error in calculation of ± 0.06°). This small amount may be ascribed to the fact that no additional solvent was used. The reaction proceeds under solvolytic-like conditions.

During solvolysis, the formation of 1-methylheptyl acetate [(R/S)-3] is also accompanied by partial racemization. As mentioned above, the reaction of (S)-1 ([α]D 20 + 5.30°) with DCC yielded (S)-2 which was converted in acetic acid to (R)-3. Subsequent hydrolysis afforded (R)-1 with a specific optical rotation, [α]D 20 - 5.18° (Table 1). Thus, under solvolytic conditions the ester formation can be expected to take place with only slight racemization (2.3%), which strongly suggests a prevailing S_n1-mechanism.

The involvement of a carbonium ion intermediate simultaneously implies the formation of minor amounts of olefinic byproducts. By GC analysis of the reaction mixtures, the expected elimination products 1-octene and (Z/E)-2-octenes were detected in considerable quantities (Table 2).

Table 2 reveals that the overall yield of olefinic byproducts ranges from 5.3 to 17.6%. Under solvolytic conditions more E1-product is formed as in the acetylsis.

With respect to ether formation, substitution via a carbenium ion is supported by the observation of further
Table 1. Reaction of Optically Active (R/S)-2 with OH Acidic Compounds

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$[\alpha]_D^{20\alpha}$</th>
<th>Product from the First Step</th>
<th>$[\alpha]_D^{20\alpha}$</th>
<th>Product from the Second Step</th>
<th>$[\alpha]_D^{20\alpha}$</th>
<th>Product(s) from the Third Step</th>
<th>$[\alpha]_D^{20\alpha}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-1</td>
<td>+10.60</td>
<td>(S)-2</td>
<td>+9.70</td>
<td>(R)-3</td>
<td>-3.74</td>
<td>(R)-1</td>
<td>-10.60</td>
</tr>
<tr>
<td>(S)-1</td>
<td>+5.30</td>
<td>(S)-2</td>
<td>+4.88</td>
<td>(R)-4</td>
<td>-12.20</td>
<td>(R)-1</td>
<td>-5.28</td>
</tr>
<tr>
<td>(S)-1</td>
<td>+5.30</td>
<td>(S)-2</td>
<td>+4.87</td>
<td>(R)-3</td>
<td>-1.81</td>
<td>(R)-1</td>
<td>-5.18</td>
</tr>
<tr>
<td>(R)-1</td>
<td>-5.30</td>
<td>(R)-2</td>
<td>-4.86</td>
<td>(S)-4</td>
<td>+12.19</td>
<td>+(+S)-5</td>
<td>+0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
| $^a$ (c = 2.0, EtOH). $^b$ Acetolysis. $^c$ (c = 0.4, EtOH).

Table 2. Yields (%) of Octenes Formed by Elimination in the Solvolysis of (R/S)-2

<table>
<thead>
<tr>
<th>Solvolysis Conditions</th>
<th>1-Octene</th>
<th>(Z)-2-Octene</th>
<th>(E)-2-Octene</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH/cyclohexane</td>
<td>1.8</td>
<td>1.3</td>
<td>2.2</td>
<td>5.3</td>
</tr>
<tr>
<td>PhOH</td>
<td>6.0</td>
<td>4.6</td>
<td>3.0</td>
<td>13.6</td>
</tr>
<tr>
<td>AcOH</td>
<td>2.6</td>
<td>-</td>
<td>-</td>
<td>17.6</td>
</tr>
</tbody>
</table>

$^a$ Based on DCU yield = 100%.

The intermediacy of carbenium ion would also result in products from hydride-shift. Indeed, gas chromatographic analysis of the product mixtures showed about 0.01% 1-ethylhexyl and 1-propylpentyl acetate, respectively, moreover 0.05% of (E)-3-octene was formed in the reaction where cyclohexane was used as the solvent. Acetolysis increased the amount of 1-ethylhexyl acetate to 0.07%, and that of 1-propylpentyl acetate to about 0.02%. Analogously in the reaction with phenol 0.07% of (Z)-3-octene, 0.03% of (E)-3-octene and less than 0.02% of (E)-4-octene, respectively, were formed.

Generally acidic reactants are necessary for alkylations with O-alkylsoureas (for exceptions see Ref. 4). It can therefore be consequently assumed that the observed transformations were catalyzed by protons which would involve a preliminary proton addition to the imine nitrogen under these reactions. This was verified by spectroscopic studies. The 1H-NMR spectrum of (RS)-2 exhibits two singlets at $\delta = 3.34$ and 2.82 for the isolated protons of the cyclohexane rings in the vicinity of the amine group and the imine group as one signal at $\delta = 3.30$ for 7. According to osmometric molecular weight measurements, 7 does no longer form a contact ion pair in 0.01 molar chloroform solutions or even more diluted solutions. When 7 was shaken with aqueous sodium hydroxide it decomposed and yielded the reactants.

byproducts. Besides (S)-4, representing the main product (70%), 1.7% of (S)+(-)-2-(1-methylheptyl)phenol [(S)-5] and 0.04% of (S)+(-)-2-(1-methylheptyl)phenol [(S)-6] were also isolated (Scheme 3). In one specific experiment it could be shown that neither of the alkyl phenols were formed by rearrangement of (S)-4. It is surprising that the generation of (R)-5 also proceeds stereospecifically. This laevorotatory phenol is formed with 97.4% inversion of configuration. The measured specific optical rotation was $[\alpha]_D^{20} = -1.45^\circ$ (c = 2.0). Whereas starting from (R)-1 with half the specific rotation we obtained the value $[\alpha]_D^{20} + 0.80^\circ$ (c = 2.0) for (S)-5 (Table 1) which corresponds with the calculated maximum specific rotation of $[\alpha]_D^{20} + 1.60^\circ$ for enantio-merically pure (S)-5.

![Scheme 3](image)

Phenol similarly forms an addition compound, (RS)-N,N'-dicyclohexyl-O-(1-methylheptyl)lisourea phenolate, with (RS)-2 which readily crystallizes from cyclohexane. The 1H-NMR spectrum of this compound exhibits a proton ratio of 1:2 for isourea/phenol and this fact was verified by microanalysis.

Large stereospecificity in the conversion of (R/S)-2 with OH acidic compounds in S$_2$N$_1$-reactions is observed for both cases described here. Under reaction conditions the optical purity exceeds for O-alkylated products to > 99.5% ee (Table 3).
<table>
<thead>
<tr>
<th>Product</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-(-)-1-methylheptyl acetate</td>
<td>100.0 ± 1.1</td>
<td>84</td>
</tr>
<tr>
<td>(R)-(+)-1-methylheptyl acetate</td>
<td>97.7 ± 2.3</td>
<td>60</td>
</tr>
<tr>
<td>(R)-(-)-1-methylheptyl phenyl ether</td>
<td>99.6 ± 2.3</td>
<td>70</td>
</tr>
<tr>
<td>(S)+(+)-J-2-(1-methylheptyl)phenol</td>
<td>94.8 ± 7.814</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* In apotropic solvents.

b Acetylation.

c C/O-ratio 1 : 40.

These promising results suggest further work as to whether similar enantioselective transformations are possible for long chain secondary alcohols. Similar investigations were performed by Kaulen10 a few years ago. A competitive method is that of Mitsuokub9 which virtually also proceeds with complete inversion of configuration. Nevertheless, these reactions demand additional auxiliary compounds which have to be used in molar quantities.

1H-NMR spectra were measured on a Varian A-60 spectrometer (CDCl3/TMS). IR spectra were recorded on a Perkin-Elmer 421 spectrophotometer and the mass spectra on an Atlas CH 4 model spectrometer (70 eV). Optical rotations were determined using a Perkin-Elmer 141 polarimeter [10 cm cell (c = 2.0, anhydrous EtOH)]. The calculated systematic error for [x]D0 amounts to ±0.06.

GC analyses were performed using Perkin–Elmer instruments 116 H (thermal conductivity detector) and F7 (FID), respectively, equipped with a Golsy capillary column [dimethyl-ethyl-cyclohexyl sebacate], carrier gas N2, and the filament was dried according to literature.20 CHCl3 and cyclohexane were dried by distilling the solvents. Activity I. 2-Octanol was distilled over a packed column prior to use: GC: 4 m glass column (polyethylene glycol), 250°C, carrier gas N2, 1.4 bar: contents of 1-octanol < 0.000 ppm, 3-octanol and 4-octanol, respectively, < 5 ppm; the racemic compound was resolved by the method of Vogel.21

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Hydrolysis of (R)-3; Typical Procedure:

From (R)-3 obtained from (S)-2, according to Method A: A mixture of (R)-3 ([x]D0 = 3.74°, 2.50 g, 14.5 mmol) and NaOH (2.00 g, 50.0 mmol) in H2O (7 ml) and EtOH (21 ml) is refluxed for 1 h. EtOH is removed by distillation, leaving two layers. The organic layer is dried on freshly calcined K2CO3 and subsequently distilled (column 25 cm) to give (R)-1: yield 1.71 g (99%); [x]D0 = 10.60°.

From (R)-3 obtained from (S)-2, according to Method B: Hydrolysis of (R)-3 ([x]D0 = 3.74°, 2.43 g, 14.1 mmol) by the above procedure affords (R)-1: yield 1.71 g (93%); [x]D0 = 10.60°.

From (R)-3 obtained from (S)-2, according to Method C: (R)-3 ([x]D0 = 1.81°, 3.2 g, 16.6 mmol) is hydrolyzed under analogous conditions to afford (R)-1: yield 2.22 g (92%); [x]D0 = 5.18°; > 99.9% pure by GC [stationary phase phenylsilicon oil, 80–140°C (2.5°C/min), carrier gas N2].

(Z)-1-(1-Methylheptyl) Pheny ether (Z)-4: (S)-2 ([x]D0 = 4.88°, 16.0 g, 47.5 mmol) and phenol (4.48 g, 47.6 mmol) are placed in a test tube which is subsequently sealed and heated at 100°C for 8 h. The contents are dissolved in CH2Cl2, DCU is filtered and washed with CH2Cl2; yield: 9.8 g (92%). After concentrating the filtrate the residue is purified by chromatography on silica gel (column 22×4.2 cm) with CH2Cl2/pentane (1:4) as eluent. UV-photometric detection allowed separation of the phenyl ether.24 The solvent is evaporated in vacuo and the crude product distilled (column 25 cm); yield 6.83 g (70%); bp 65–66°C/0.004 mbar (Lit.23 bp 144–145°C/27 mbar); nD20 1.4863 (Lit.23 nD20 1.4878); [x]D0 = 12.20°.

IR (film): v = 3096, 3060, 3040, 3030, 2960, 2870, 2930, 2860, 1598, 1493, 1465, 1380, 1240, 1025, 880, 750, 695 cm−1.

1H-NMR (CDCl3/TMS): δ = 0.88 (t, 3H, CH3), 1.27 (d, 3H, J = 5.5 Hz), 3.18 (mc, 10H, CH2), 4.33 (mc, 1H, CH), 7.05 (6H, CH3).
and the combined extracts are concentrated on a rotary evaporator yielding a residue which is purified by distillation (column 25 cm) to give (R)-1 yielding 1.2; yield: 13.4 g (31%) [2]Dr = 5.28; > 99.9% pure by GC [stationary phase: phenylsilicon oil, 130–190°C (5°C/min), carrier gas N2].

(S)-(+)-2- and (S)-(−)-4-(1-Methylheptyl)phenol [(S)-5]; (S)-6: A mixture of (R)-2–(2) [2]D = 4.86, 31.4 g, 93.5 mmol) and phenol (8.80 g, 93.6 mmol) is heated in an ampule at 100°C for 16 h. The mixture is dissolved in CH2Cl2 and the DCM removed by filtration. The concentrated filtrate is chromatographed on basic Al2O3 (column 60 × 5.5 cm, CH2Cl2/pentane). (S)-4 is separated as the first fraction: yield: 13.5 g (70%); [2]D = −12.19 (c = 2.0). The phenolic components are eluted with MeOH, the eluent is removed by distillation, and the residue dissolved in petroleum ether (15 mL). Unconverted phenol crystallizes and is filtered. The residual concentrate is subsequently separated on silica gel column (20 × 3.5 cm; CH2Cl2). Three fractions are collected [R, 0.56, (S)-5; R = 0.31, (S)-6; R = 0.26, phenol; TLC: silica gel/CH2Cl2]. The first fraction (R = 0.56) is concentrated and the residue eluted twice on silica gel [column 23 × 2.2 cm; CH2Cl2/pentane (1:1)]. From the eluate (S)-5 is isolated by rotary evaporation whereby solvent traces are carefully eliminated in vacuo; yield: 25.7 mg (1.7%); [2]D = 0.80 (c = 2.0); [2]D = 1.60 (c = 0.4); purity > 99.6% by GC (stationary phase: trimethylsilyl tripropargylate, 200°C, carrier gas N2, r = 67 min). The compound is identical with the rac. material.

IR (film): v = 3430, 3060, 3030, 2955, 2925, 2870, 2855, 1608, 1590, 1503, 1490, 1453, 827, 750 cm−1. 1H-NMR (CDCl3/TMS): δ = 0.85 (t, 3H, CH3), 1.22 (d, 3H, J = 7.5 Hz, CH3), 1.43 (mc, 10H, CH2), 2.90 (m, 1H, CH), 4.92 (s, 1H, OH, exchangeable with D2O), 6.79 (m, 4Hvom). MS (70 eV): m/z (%) = 206 (M+, 11), 122 (7), 121 (100), 107 (8), 103 (6), 91 (7), 57 (7).

The second fraction (R = 0.31) is further monitored by TLC. The compound having R, 0.45 [silica gel; CH2Cl2/pentane/MeOH (49:49:2)] is separated by preparative TLC on silica gel PF 254–366; Merck [CH2Cl2/pentane/MeOH (48:75:25:2.5)]. The product containing fraction is extracted with CH2Cl2 and filtered. The solvent is removed by rotary evaporation and traces of solvent are carefully eliminated in vacuo; yield: 7.5 mg (S)-6 (0.04%); [2]D = 15.00 (c = 0.4). IR (CCl4): v = 3604, 3006, 2995, 2930, 2870, 2855, 1878, 1614, 1595, 1510, 1455–1468, 1435, 1380, 1234, 1255, 1171, 720–820 cm−1. 1H-NMR (CDCl3/TMS): δ = 0.38 (m, 3H, CH3), 1.20 (d, 3H, J = 8.5 Hz, CH3), 1.42 (mc, 10H, CH2), 2.54 (m, 1H, CH), 4.60 (s, 1H, OH, exchangeable with D2O), 6.78, d, 2Hvom, J = 9 Hz), 7.06 (d, 2Hvom, J = 9 Hz). MS (70 eV): m/z (%) = 206 (M+, 5), 122 (10), 121 (100), 107 (11), 103 (4), 91 (4), 77 (6).

(RS)-N,N-Dicyclohexyl-O-(1-methylheptyl)isouromium Phenate [(RS)-2·2·2-phOH]: A solution of (RS)-2 (5.50 g, 16.3 mmol) and phenol (1.54 g, 16.4 mmol) in cyclohexane (4 mL) is cooled to 3°C, and the precipitated crystals are filtered; yield: 3.1 g (36%), 1H-NMR (CDCl3/TMS): δ = 0.95 (t, 3H, CH3), 1.18 (d, 3H, J = 5 Hz, CH3), 1.63 (mc, 30H, CH2), 3.20 (m, 2H, CH), 4.84 (m, 2H, CH), 7.00 (m, 10Hvom), 7.51 (s, 3H, 2NH–OH, exchangeable with D2O). I am indebted to Prof. Dr. E. Vowinkel for the support of this work. Financial support by the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

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(14) Vowinkel, E.; Deiterding, H., unpublished results.

(15) These workers started their investigations with (S)-1 [x]D = +10.10 (c = 2.0, EtOH)] and for laevorotatory 5 they obtained the specific rotation [x]D = −1.45°. The difference of the values [x]D = +10.10 to +10.60 for (S)-1 amounts to 4.2%. Considering the difference for laevorotatory phenol they should have obtained [x]D = −1.53°. This value is used now for the calculations of stereospecificity. Furthermore the absolute configuration of laevorotatory 5 was determined to be (R) by 1H-NMR spectrometric investigations using the chiral shift reagent tris(+)-camphorato-3-(tert-butylhydroxymethyl)europiumIII (optical purity 94.6% ± 8.3%).


(18) (Z)-4-Octene almost co-elutes with 1-octene. Both octenes exhibit nearly identical retention time on the applied column.

(19) Similar diastereom compounds were obtained in the reaction of halophenols with DCC. Kovacs, J.; Kifaludy, L.; Ceprini, M. Q. J. Am. Chem. Soc. 1967, 89, 183.


(24) UV-photometric detection.
(26) IR and mass spectra of (S)-5 are identical in spectroscopic characteristics with rac-2-(1-methylpropyl)phenol.