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First example of axial selectivity in the nucleophilic addition to (–)-menthone—addition of cyanomethyl lithium†

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Abstract

The addition of cyanomethyl lithium to (–)-menthone at –78°C followed by 1.5 h stirring at room temperature and acidic workup produced exclusively the axial addition product, being the first example of preferred axial attack of an organometallic reagent to menthone. In the case of hydrolysis at –78°C after 0.5 h reaction time the equatorial addition product was isolated as the preferably formed isomer. The axial and equatorial cyanomethyl substituted menthol and neomenthol, respectively, were isolated in high yields.

1. Introduction

The addition of organometallic compounds to menthone has been described to proceed exclusively from the equatorial face of the carbonyl carbon atom.[1,2] We have recently prepared a chiral δ-aminoalcohol as a result of the equatorial attack of dimethylaminopropyl lithium to (–)-menthone,[3] being interested in the preparation of ligands for asymmetric syntheses.[4] In further experiments[5] we investigated the addition of different organometallic reagents to (–)-menthone obtaining new chiral nonracemic compounds as a result also of exclusively equatorial attack. An equatorial selectivity for the nucleophilic addition of the acetonitrile anion to menthone has been reported by Trost et al.[6] as an example demonstrating the limitation to the preference for axial attack of this reagent to several cyclic ketones.[6,7]

2. Results and discussion

We were interested in the preparation of 1-hydroxy-2-isopropyl-5-methyl-cyclohex-1-yl-acetonitrile for further synthetic applications and could obtain mainly the equatorial addition product

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† Dedicated to Professor Dr. Manfred Hesse on the occasion of his 65th birthday.

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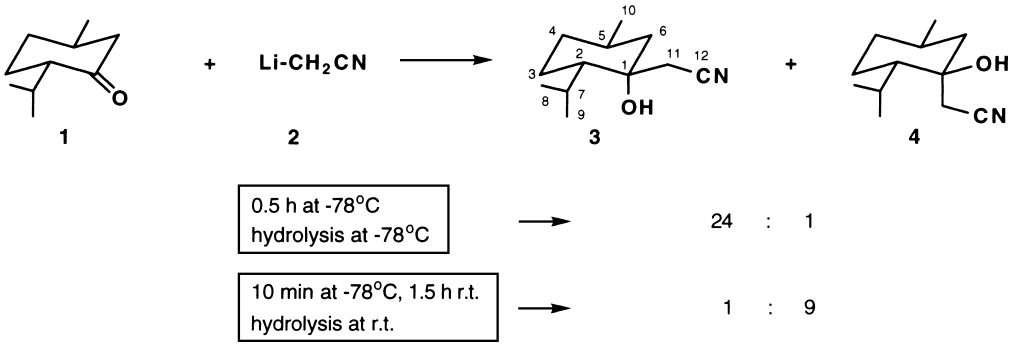
3 after performing the reaction between (–)-menthone and $LiCH_2CN$[8] in THF at –78°C for 0.5 h and hydrolyzing the reaction mixture at this temperature (see Scheme 1 and Experimental). The ratio of the diastereoisomers **3** and **4** obtained was in accordance with the results published by Trost et al.[6] However, when the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h the ratio of the isomers in the crude product, obtained after hydrolytic workup, was **3**:**4** = 1:9 (Scheme 1). To the best of our knowledge this is the first example of predominantly axial addition attack of organometallic reagent to menthone. These results indicate a higher thermodynamic stability of compound **4** formed in the course of the reversible addition reaction at room temperature from the initially predominant product **3**. Some evidence for reversibility has been published.[1h] Therefore compound **3** should be a result of a kinetically controlled addition reaction.



Scheme 1.

The differences in the stereochemical course of the addition reactions should not be argued with conformational changes in menthone depending on the temperature (e.g. ring flipping leading to a conformer with axial positioned isopropyl and methyl groups), since by means of vibrational circular dichroism,[9] as well as NMR and molecular modelling studies,[10] the dominant conformer of **1** has been determined as those depicted in Scheme 1. It seems that the reagent $LiCH_2CN$ is responsible for the observed differences in the stereoselectivity, since with other reagents the equatorial addition has always been preferred.[1–3] $LiCH_2CN$ has been suggested by theoretical studies to exist in solution both as solvated eight-membered ring dimers bridged by lithium and as solvated ketimine dimers (with lithium attached to the nitrogen).[11] Cyanomethyl lithium can effectively interconvert on aggregation and solvatation into the ketimine form.[11] The ketimine form of the reagent, having a lower steric bulk, was proposed by Trost et al.[6] to be responsible for the reported axial attack on some cyclic ketones. However, no experimental structural information is available for $LiCH_2CN$ so far and it is only known for it to exist between –108°C and room temperature as a dimer, based on cryoscopy and NMR studies.[11]

The cyanomethyl derivative **4** could be obtained as a pure diastereoisomer after crystallization; however, this was not possible for product **3**. The observed value of the specific rotation for **3** is therefore a result of the influence caused by compound **4** (see Experimental).

The addition of $LiCH_2CN$ as a solid reagent[8a] to (–)-menthone at room temperature followed by hydrolysis after 5 min provided mainly unreacted ketone **1**, a small quantity of the addition products **3** and **4**, and surprisingly isomenthone (**1**:isomenthone:products **3**/**4** = 70:17:13; ratio **3**:**4** = 1:10; the isopropyl and the methyl groups in isomenthone are *cis* positioned). The observed

epimerization of (–)-menthone is probably the result of enolization. We tried to prove this assumption by deuterolysis with D_2O of the reaction mixture after addition of $LiCH_2CN$ at room temperature. However, we could not find by NMR any deuterium labelled menthone and isomenthone. Epimerization of (–)-menthone has also been reported to proceed easily by the reaction with tosylhydrazine to the corresponding menthonetosylhydrazone.[12]

In conclusion, we have observed an unusual axial addition selectivity of acetonitrile lithium to (–)-menthone. The variation of the reaction conditions allowed us to synthesize both axial and equatorial addition products on a preparative scale.

3. Experimental

3.1. (1R,2S,5R)-1-Hydroxy-2-isopropyl-5-methylcyclohex-1-yl-acetonitrile **3**

To a stirred solution of 1.80 ml (4.12 mmol) 2.29 M *n*-BuLi in hexane and 4 ml THF were added 0.20 g (4.87 mmol) CH_3CN in 2 ml THF at –78°C and the mixture was stirred for 45 min at this temperature. After that 0.54 g (3.50 mmol) of **1** in 2 ml THF were added, the mixture stirred for 0.5 h at –78°C and hydrolyzed (2N HCl) at this temperature. It was extracted with Et_2O (3×15 ml), the organic layer washed with 5% aq. $NaHCO_3$, H_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product 0.68 g (quant.) was pure by TLC and NMR (diastereoisomeric ratio **3**:**4** = 24:1). Mp 50–52°C. $[\alpha]_D^{20}$ 0 (c = 1.12, $CHCl_3$), $[\alpha]_D^{20}$ +1.6 (c = 1.03, EtOH). Anal. calcd for $C_{12}H_{21}NO$ (195.30): C, 73.80; H, 10.84; N, 7.17. Found: C, 73.57; H, 10.59; N, 7.03. MS (CI: NH_3) m/z (%): 213 ($[M+18]^+$, 100), 196 ($[M+1]^+$, 2). ^1H NMR (250 MHz, $CDCl_3$, 300 K): δ = 0.78–0.97 (m, 1H, 4-H_{ax}), 0.92 (d, 3H, 10-H, J = 6.9 Hz), 0.92 (d, 3H, 8-H, J = 5.9 Hz), 0.96 (d, 3H, 9-H, J = 6.9 Hz), 1.29 (t, 1H, 6-H_{ax}, J = 12.00 Hz), 1.31 (dm, 1H, 2-H_{ax}), 1.41 (qd, 1H, 3-H_{ax}, J = 12.5, 3.2 Hz), 1.55–1.60 (m, 1H, 3-H_{eq}), 1.57 (s, 1H, OH), 1.60–1.78 (m, 1H, 5-H_{ax}), 1.80 (dm, 2H, 4-H_{eq}, 6-H_{eq}), 2.02 (quintd, 1H, 7-H, J = 6.9, 1.7 Hz), 2.58 (d, 1H, 11-H_a, J = 16.6 Hz), 2.66 (d, 1H, 11-H_b, J = 16.6 Hz) (Table 1).

Table 1
^{13}C NMR chemical shifts for compounds **3** and **4** in $CDCl_3$

No. C-atom* / Compound	1	2	3	4	5	6	7	8	9	10	11	12
3	73.65	48.13	20.30	34.40	27.65	47.37	26.16	17.75	23.28	21.79	29.98	117.78
4	73.31	52.26	24.00	34.43	30.13	48.34	24.72	19.08	24.37	21.93	24.14	117.95

*Assignments are based on heteronuclear CH-correlation experiments (HSQC)[13]; for the numbering of the C-atoms see Scheme 1.

3.2. (1S,2S,5R)-1-Hydroxy-2-isopropyl-5-methylcyclohex-1-yl-acetonitrile **4**

To a stirred solution of 3.32 ml (7.60 mmol) 2.29 M *n*-BuLi in hexane and 4 ml THF were added 0.34 g (8.28 mmol) CH_3CN in 2 ml THF at –78°C and the mixture was stirred for 45 min at this temperature. After that 0.90 g (5.83 mmol) of **1** in 4 ml THF were added, the mixture stirred for 10 min at –78°C and then allowed to warm to rt. It was stirred for 1.5 h at rt, hydrolyzed (2N HCl) and extracted with Et_2O (3×20 ml). The organic layer was washed with 5%

aq. $NaHCO_3$, H_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product, 1.17 g (**3**:**4** = 1:9 by NMR), was recrystallized from hexane to give 0.77 g (68%) of pure **4** as colorless crystals. Mp 105–106°C. $[\alpha]_D^{20}$ –34.4 ($c = 1.01$, $CHCl_3$), $[\alpha]_D^{20}$ –31.1 ($c = 1.04$, EtOH). Anal. calcd for $C_{12}H_{21}NO$ (195.30): C, 73.80; H, 10.84; N, 7.17. Found: C, 73.71; H, 10.64; N, 7.12. MS (CI: NH_3) m/z (%): 213 ($[M+18]^+$, 100), 196 ($[M+1]^+$, 2). ^1H NMR (250 MHz, $CDCl_3$, 300 K): $\delta = 0.81$ (d, 3H, 8-H, J = 6.8 Hz), 0.88–0.98 (m, 1H, 4-H_{ax}), 0.93–1.05 (m, 1H, 3-H_{ax}), 0.95 (d, 3H, 10-H, J = 6.6 Hz), 1.00 (d, 3H, 9-H, J = 7.1 Hz), 1.09 (t, 1H, 6-H_{ax}, J = 12.7 Hz), 1.31 (dt, 1H, 2-H_{ax}, J = 12.0, 3.2 Hz), 1.35–1.52 (m, 1H, 5-H_{ax}), 1.72 (dm, 1H, 3-H_{eq}), 1.78 (dm, 1H, 4-H_{eq}), 2.10 (quintd, 1H, 7-H, J = 6.9, 2.2 Hz), 2.15 (dm, 1H, 6-H_{eq}), 2.62 (s, 2H, 11-H).

The addition of $LiCH_2CN$ at rt occurred with a rapid introduction of the isolated solid reagent[8a] to a solution of (–)-menthone in THF.

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