Synthesis and Characterization of Enantiomerically Pure Menthylamines and Their Isocyanates

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Abstract: A synthetic protocol for optically pure (–)-menthylamine, (–)-8-methylmenthylamine, and the novel (–)-8-phenylmenthylamine is presented including a detailed characterization of these compounds and their isocyanates.

Key words: amines, aminations, asymmetric synthesis, chirality, chiral auxiliaries

Enantiomerically pure α-chiral amines 1 are important building blocks and auxiliaries in synthetic organic chemistry.1 Several methodologies are established for the enantioselective synthesis of these compounds.2 If very bulky substituents on the α-stereogenic center are involved, common procedures like the conversion of enantiopure sulfinimines suffer from low yields and are consequently less attractive.3 For our supramolecular investigations, α-chiral amines with far-projecting substituents (R2) larger than tert-butyl groups (e.g. 2) were required. The chiral information should be addressed by steric means in the vicinity of the nitrogen. In addition, the rigidity of the cyclohexane skeleton will provide conformational stability with locating the substituents appropriately and resulting in different steric demands on both sides of the nitrogen.4 All these molecular features are excellently combined in 3 (Figure 1).

Optically pure menthylamine or 8-substituted derivatives 3 seemed to be the compounds of choice since an ex chiral pool synthesis can be exploited and should be feasible on a multi-gram scale. 8-Substituted (–)-menthol derivatives are widely used auxiliaries e.g. in the Diels–Alder reaction.5 In contrast, the corresponding menthylamines are either not known or only sparingly described in the literature.6,7

We describe a reliable protocol for the synthesis of enantiopure menthyl-, 8-methylmenthyl-, and 8-phenylmethylnylamine, as well as their isocyanates, including the full analytical characterization. All transformations can be applied to multi-gram quantities.

The synthesis of the parent menthylamine started directly with the commercially available (–)-menthone. For the 8-substituted derivatives the corresponding menthones had to be prepared first. Therefore, we used (+)-pulegone (4) and installed the appropriate moiety by cuprate addition, providing 5b/c (Scheme 1).8 Employment of (+)-pulegone in practical grade (92%) is recommended since the impurities and the by-products of the 1,4-addition are easily removed after the transformation. The 1,2-addition occurred in a side reaction forming the intermediate alcohols, which undergo elimination upon work-up. The menthanones 5b/c were purified by a single distillation and consisted of an epimeric mixture due to the configurational labile α-carbon.

Subsequent oxime formation (Scheme 2) was performed under standard conditions.9 Analytically pure product was only obtained after column chromatography on silica yielding 6a–c as colorless crystals. At the beginning, the eluent contains pure (E)-oxime; only the last 20% of the eluent consists of an E/Z-mixture. Therefore, all analytical data refer to the (E)-oxime. While the menthyl and 8-phenylmethyl oxime resulted in excellent yields, the 8-methylmenthyl derivative 6b was obtained only in less quantity. The known physical data for 6a/b are restricted to their melting points,6,7 which was confirmed for 6a. For the oxime 6b we found a quite different melting point.10 The significant impact of the substitution pattern in the 8-position of the menthane skeleton is revealed in different yields when a chemical reaction is performed directly on the cyclohexane moiety. Consequently, the reduction of
the oximes followed by a Beauvaul–Blanc reaction provided the amines 3a/c in good yields, but the transformation of the 8-methylmenthol oxime 6b required prolonged reaction times. The individual amines 3 were formed as single products when using sodium and alcohol as a reductive mixture. Unfortunately, the conversion stops when the resulting salts precipitate. Furthermore, applying larger amounts of sodium metal is difficult and dangerous since encrustation of metallic material will occur. Switching to other proton sources like tert-butanol, 2-propanol or amyl alcohol did not ameliorate the problems. The crude amines 3 were purified by vacuum distillation wherein the corresponding oxime was reisolated. We made efforts to substitute the Beauvaul–Blanc reaction by catalytic reductions. When 6b was treated with heterogeneous transition metal catalysts, like CoCl₂-NaBH₄, NiCl₂-NaBH₄, PtO₂-H₂, Raney-Ni, or Pd/C-H₂, either no conversion was found or the corresponding amine 3b was accompanied by an equal amount of a diastereomeric amine. The separation of these epimeric amines did not succeed on a preparative scale.

For the preparation of the isocyanates, the amines were converted into the ammonium salts and subsequently treated with phosgene. For analytical purposes, all ammonium salts were recrystallized from dioxane, which rendered a lower yield given in Scheme 2 as first crop. Subsequent crops from the mother liquor indicated small impurities and were not used further. For various reactions and as a stable form for storage the solid hydrochlorides turned out to be ideal and were consequently used for detailed analytical studies. When applying the crude ammonium salts to the phosgenation, a significantly higher yield was observed. All isocyanates 8b were colorless, viscous liquids. The unusually high steric hindrance of the nitrogen in the 8-methylmenthol system is demonstrated in the isocyanate 8b which reacts very slowly and is therefore less prone to hydrolysis.

Remarkably, all menthyl derivatives, except 6b and 9, show a negative optical rotation in the measured light range (365–589 nm). The absolute configurations of the menthyl isocyanates 8a/b were confirmed by X-ray analyses after installing them onto receptor moieties.¹ The expected (1R,3R,4S)-configuration was verified.¹¹ Since the 8-phenylmenthol isocyanate 8c and its precursors did not give any suitable crystal for X-ray analysis, we converted 7c to the 4-nitrobenzoic amide (Scheme 3), which gave excellent crystals for determining the solid state structure (Figure 2). The anticipated π–π-interaction between the phenyl and the 4-nitrophenyl system is not observed in the crystal. In the solid state the electron poor nitro arene is embedded by two cyclohexane moieties, which is most likely caused by packing effects.

When locating bulky groups in the vicinity of functional groups and studying secondary interactions between these systems a correct assignment of the individual NMR signals is crucial. Therefore, we performed a complete analytical characterization by NMR including multidimensional techniques. For the assignment of all ¹H NMR signals we started with the well-separated signal set on C-1 and C-3, respectively. The combination of characteristic coupling patterns and correlated spectra identified the remaining signals. Heteronuclear correlation provided a clear assignment for the ¹³C signals. Both, the functional group in the 3-position and the substituent on the exocyclic moiety have a significant impact on the spectra. Consequently, the corresponding multiplets differ strongly in

![Scheme 2](image_url)

the chemical shifts as well as in their shape. A complete set of correlated spectra is given in detail for 3a and 8a, which can be exemplarily employed for the spectral assignment of the other compounds. Sufficient NMR resolution was achieved on a 600 MHz instrument.

In conclusion, we developed reliable protocols for the synthesis of (−)-menthylamine, (−)-8-methylmenthylamine and the novel (−)-8-phenylmenthyl system. These very bulky optically pure α-chiral amines are readily accessible on a multi-gram scale, starting from (−)-menthol or (+)-pulegone, respectively. Furthermore, the corresponding isocyanates were established as highly active equivalents of these particular amines. For the first time, a comprehensive analytical study for this class of compounds was performed. NMR spectroscopy and X-ray analysis gave a consistent stereochemical picture. All NMR signals for the primary amines 3 and its derivatives 6–8 were assigned. The use of these particular auxiliaries will be reported in due course.

All reagents were used in analytical grades. Solvents were desiccated if necessary by standard methods. Column chromatography was performed on silica gel (particle size 63–200 μm). Chromatography was achieved on a 600 MHz instrument.

PAPER

Enantioselectively Pure Methylamines and Their Isocyanates

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Reduction to (−)-Menthylamines (3); General Procedure
A 500 mL two-necked flask equipped with a metal condenser, argon inlet and septum was charged with sodium (8.5 g, 368 mmol) and anhyd toluene (200 mL). The mixture was refluxed for 15 min forming a finely dispersed system to which the oxime 6 (18.4 mmol) was injected as a toluene solution. After 15 min, EtOH (30 mL) was added dropwise. The reaction was monitored by GC and additional sodium and EtOH were added if necessary. After all metallic sodium has been dissolved, the reaction mixture was acidified to pH 1 at 0 °C (caution!) using concd aq HCl. Subsequently, the solvents has been dissolved, the reaction mixture was acidified to pH 1 at 0 °C (caution!) using concd aq HCl. Subsequently, the solvents were removed under reduced pressure. With NaOH-solution (20%) the pH was adjusted to 12 and the aq layer was extracted with EtOAc (6 × 100 mL). After drying (NaOH), the organic layer was concentrated and purified by distillation yielding the amines 3 as colorless oils. A higher boiling fraction consisted of the corresponding starting materials 6.

(−)-(1R,3R,4S)-Menthylamine (3a)
Yield: 1.7 g (10.9 mmol, 59%); bp 74–77 °C (11–13 mbar); [α]25D −35.7 (c 0.1, CHCl3); 1H NMR (600 MHz, CDCl3): δ = 0.78 (m, 2 H, 2, 6-Ha), 1.07 (m, 1 H, 1-Ha), 1.12 (m, 1 H, 4-Ha), 1.38–1.46 (m, 1 H, 5-Ha), 1.60 (m, 1 H, 5-Ha), 1.82–1.84 (m, 3 H, 2-Ha, NH), 2.81–2.84 (m, 1 H, 3-Ha), 8.19 (s(w), 3 H, NH).

13C NMR (150 MHz, CDCl3): δ = 15.9 (C-3), 21.2 (C-10), 22.3 (C-7), 23.1 (C-5), 25.9 (C-8), 31.9 (C-1), 34.8 (C-6), 45.5 (C-2), 50.3 (C-4), 51.5 (C-3).

GCOSY (600 MHz/600 MHz, CDCl3): δ (H/δ (H) = 0.78 (9H, 2.90–2.14 (4H)), 0.81–0.88 (2H, 2.43–2.49 (4H, 5-Ha)), 0.80 (4H, 1.41–1.50 (4H, 5-Ha)), 1.20 (6-Ha), 1.21–1.82 (4H, 2.44–2.45 (4H, 5-Ha)), 0.87 (2H, 1.38–1.46 (4H, 1-Ha)), 0.93–1.00 (2H, 2.09–2.14 (4H)), 0.94–0.99 (4H, 5-Ha), 1.60 (5-Ha), 1.68–1.70 (6-Ha), 1.71 (3-Ha), 1.78–2.45 (3-Ha), 2.81–2.84 (1H, 3-Ha).

(−)-(1R,3R,4S)-8-Methylmenthylamine (3c)
Yield: 5.1 g (26.4 mmol, 66%); mp 187 °C (sublimation); [α]24D −38.1 (c 0.1, CHCl3); 1H NMR (600 MHz, CDCl3): δ = 0.78 (d, 3 H, 1-Ha), 1.07 (m, 1 H, 4-Ha), 1.12 (m, 1 H, 5-Ha), 1.38–1.46 (m, 1 H, 5-Ha), 1.56 (m, 1 H, 2-Ha), 1.64 (m, 1 H, 5-Ha), 1.71 (m, 1 H, 6-Ha), 1.82–1.84 (m, 3 H, 2-Ha, NH), 2.81–2.84 (m, 1 H, 3-Ha).

13C NMR (150 MHz, CDCl3): δ = 12.2 (C-7), 27.3 (C-5), 29.7 (C-9), 31.9 (C-1), 33.8 (C-6), 48.1 (C-2), 53.3 (C-3/4).

MS (EI, 70 eV): m/z (%) = 169.2 (20) [M+], 151.4 (7) [M+ – CH3], 112.1 (4) [C6H7N+], 95.0 (3) [112 + – NH], 70.0 (100) [C6H10], 75.0 (6) [C6H9+].

Anal. Calc'd for C11H23N (169.31): C, 78.03; H, 13.69; N, 8.27. Found: C, 78.01; H, 13.70; N, 8.28.

(−)-(1R,3R,4S)-8-Methylmenthylammonium Chloride (7a)
Yield: 2.1 g (12.3 mmol, 67%); bp 98–102 °C (28–30 mbar); [α]25D −26.6 (c 0.1, CHCl3); 1H NMR (600 MHz, CDCl3): δ = 0.82 (d, 1 H, 6-Ha), 3.6 (J = 12.6 Hz), 0.87 (d, 3 H, 7-Ha, J = 6.6 Hz), 0.88–0.93 (m, 2 H, 2-Ha, 4-Ha), 0.97 (d, 1 H, 5-Ha), 3.6 (J = 13.2 Hz), 1.00 (s, 9 H, 9-H), 1.17 (s(w), 2 H, NH), 1.35–1.44 (m, 1 H, 1-Ha), 1.66 (d, 1 H, 6-Ha), 3.6 (J = 3.6, J = 12.6 Hz), 1.71 (d, 1 H, 5-Ha), 3.6 (J = 3.6, J = 13.2 Hz), 1.78 (d, 1 H, 5-Ha), 3.6 (J = 3.6, J = 13.2 Hz), 2.63 (d, 1 H, 3-Ha), 3.6 (J = 3.6, J = 10.2 Hz).

13C NMR (150 MHz, CDCl3): δ = 22.2 (C-7), 27.3 (C-5), 29.7 (C-9), 31.9 (C-1), 33.8 (C-6), 48.1 (C-2), 53.3 (C-3/4).

MS (EI, 70 eV): m/z (%) = 169.2 (20) [M+], 151.4 (7) [M+ – CH3], 112.1 (4) [C6H7N+], 95.0 (3) [112 + – NH], 70.0 (100) [C6H10], 75.0 (6) [C6H9+].


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(1R,3R,4S)-8-Phenylmenthylammonium Chloride (7c)

Yield: 7.93 g (29.6 mol%, 74%); m p 198 °C (sublimation); \[
\delta = 18.3, \ \delta_{\text{cr}} = -19.1, \ \delta_{\text{ga}} = -21.6. \ \delta_{\text{ga}}^{(15)} = -34.7, \ \delta_{\text{ga}}^{(15)} = -49.0 \ (c, 1.02, MeOH).
\]

^1H NMR (400 MHz, DMSO-\text{d}_6); \delta = 0.60 (ddd, 1 H, 6-\text{H}, \ \delta_{\text{ga}}^{(6)} = 2.8, \ \delta_{\text{ga}}^{(6)} = 12.8 \text{ Hz}), 0.80 (d, 3 H, 7-\text{H}, \ \delta_{\text{ga}}^{(7)} = 6.4 \text{ Hz}), 0.90 (m, 1 H, 5-\text{H}), 1.05—1.15 (m, 2 H, 2-\text{H}, 5-\text{H}), 1.26 (3, s, 3 H, 9-\text{H}), 1.31—1.39 (m, 2 H, 1-\text{H}, 6-\text{H}), 1.44 (3, s, 3 H, 10-\text{H}), 1.96 (ddd, 1 H, 4-\text{H}, \ \delta_{\text{ga}}^{(4)} = 2.8, \ \delta_{\text{ga}}^{(4)} = 11.6, \ \delta_{\text{ga}}^{(11)} = 15.2 \text{ Hz}), 2.09 (ddd, 1 H, 2-\text{H}, \ \delta_{\text{ga}}^{(2)} = 11.2 \text{ Hz}), 2.09 (m, 1 H, 1-\text{H}), 7.13—7.17 (m, 1 H, Ar-H, 7.26—7.30 (m, 3 H, Ar-H), 8.04 (s[w], 3 H, NH).

^13C NMR (100 MHz, DMSO-\text{d}_6); \delta = 21.8 (C-7), 22.6 (C-9), 27.3 (C-5), 29.2 (C-10), 30.9 (C-1), 33.9 (C-6), 40.5 (C-2), 41.2 (C-8), 49.6 (C-4), 51.9 (13C), 125.5, 125.7, 128.4, 150.8 (C-Ar).

MS (ESI): \text{m/z} = 232.2 (M–H).


Phosgenation; General Procedure

The menthylammonium chlorides \(R\)-(-)(1-c)-1R,3R,4S-8-Phenylmenthylammonium Chloride (7c) were obtained by the reaction of menthol with excess phosgene in the presence of ammonia. All glassware was treated thoroughly with acetic acid before use. The defrosting of the trapped contents should be performed in the presence of ammonia. All glassware was treated thoroughly with acetic acid before use. The defrosting of the trapped contents should be performed in the presence of ammonia. All glassware was treated thoroughly with acetic acid before use. The defrosting of the trapped contents should be performed in the presence of ammonia. All glassware was treated thoroughly with acetic acid before use.
(m, 1 H, H-1), 1.42 (s, 3 H, 9/-10-H), 1.54–1.62 (m, 2 H, 5-H e , 6-H e ).
13C NMR (100 MHz, CDCl3): 172.12 (C-17), 129.0 (C-13), 139.4 (C-16), 149.1 (C-19), 153.1 (C-11), 143.1 (C-18), 125.0 (C-12), 125.3 (C-14), 127.7 (C-8).

Anal. Calcd for C23H28N2O3: C, 72.60; H, 7.42; N, 7.36.

References