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The Epimerization of α-Chiral Hydrazones: Menthonetosylhydrazone.

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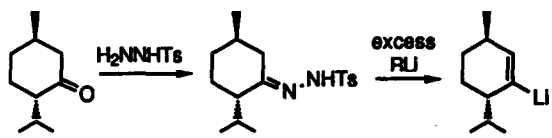
Abstract: The first preparation of (-)-menthonetosylhydrazone (2) in diastereomerically pure form is reported. Kinetic studies show that 2 is far more susceptible to acid-catalyzed epimerization (~150x) than is the parent ketone, (-)-menthone (1), a relationship which has not been generally recognized. Conversion of 2 to 1-menthenyllithium (3) using excess butyllithium occurs without detectable epimerization, as determined by analysis of the 1-iodomenthene 5 obtained by treatment of 3 with iodine *in-situ*.

Hydrazones are versatile intermediates by which ketones can be manipulated in several useful ways.[1] In particular, ketone tosyhydrazones may be converted into vinyllithiums and related materials via the Shapiro reaction.[2] Several other methods for this type of conversion are known, involving trisylhydrazones,[3] enol triflates,[4] or phenyl vinyl sulfides,[5] although these procedures often require expensive reagents[3,4] or lack regioselectivity in the case of unsymmetrical ketones.[5] A related, multistep procedure which results in a 1,2-transposition of functionalilty was recently reported.[6] Such conversions of α-chiral ketones, such as menthone (1), are complicated by the need to avoid epimerization if one is to obtain enantiomerically or diastereomerically-pure products. Here we wish to report that while menthonetosylhydrazone (2) can be prepared diastereomerically pure under appropriate conditions, it undergoes epimerization far more readily than the parent ketone and that the epimerized hydrazone is the *more stable* isomer.

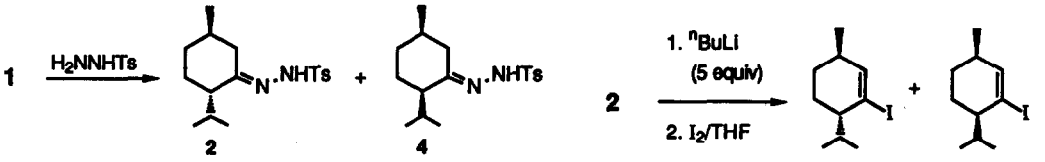


1 2 3

(-)-Menthone (1) is one of the most readily available[7] enantiomerically pure terpenoid ketones, and Shapiro conversion of the tosyhydrazone to the corresponding vinyllithium (3) would allow one to incorporate this fragment into a variety of structures. The preparation of menthonetosylhydrazone has been described only twice in the literature,[8] and the product was characterized only by melting point. The literature preparation[8a] involves heating menthone and tosylhydrazine in ethanol (reflux, 1.5 hrs). In our hands, this approach yielded an equilibrium mixture of two hydrazones in a 71:29 ratio (HPLC). A crystal suitable for X-ray analysis[9] was obtained from this mixture, and proved to be that of the cis hydrazone 4. HPLC analysis of the X-ray crystal and the mixture showed that the cis hydrazone 4 was the *major* isomer present under these conditions. As described below, the minor isomer was identified as the trans hydrazone 2. Recrystallization of this mixture from ethanol did not significantly improve the purity.

Since we desired the diastereomerically pure trans hydrazone 2, we sought reaction conditions under which it could be prepared without epimerization. We found that the reaction of menthone and tosylhydrazine in the

presence of any amount of acid (e.g., conc. HCl), even at 0 °C, led to mixtures of hydrazones **2** and **4**. Heating, even in the absence of acid, also promoted formation of **4**. However, in the absence of acid in cold dichloromethane (0 °C, 2 hrs), the reaction proceeded with little or no epimerization, yielding the trans hydrazone **2** in 76-91% yield. A small amount (2-4% by HPLC) of cis isomer **4** was also apparent, but this could be attributed largely to the presence of traces (2-3% by GC) of isomenthone in commercial (-)-menthone,[7] rather than to epimerization during hydrazone formation. The stereochemistry of **2** was confirmed by X-ray analysis.[9] The ^{1}H NMR ($CDCl_3$) supported the solid-state structure, showing that the methyl group on C-5 was equatorial, since one of the CH_2 protons α to the C=N exhibited a large axial-axial coupling (10.7 Hz). Similar couplings have been reported for the parent ketone.[10] Using Fuch's method,[11] it was also clear by NMR that hydrazone **2** exists in the E configuration with respect to the C=N double bond, since the α-CH_2 carbon in **2** shifts upfield by 16.1 ppm relative to menthone, while the α-CH changes by only 5.3 ppm. Hydrazone **2** appears to be stereochemically stable indefinitely in the solid state when stored at 0 °C, but is less stable in solution.[12a]



conditions:
(a) refluxing ethanol, 1.5 hrs 2:4 = 29:71, 72% yield
(b) dichloromethane, 0°C, 2 hrs 2:4 = > 96:4, 76-91% yield

We have observed that tosylhydrazone **2** is much more sensitive to acid-catalyzed epimerization than is the parent ketone **1**. For example, treatment of a 0.2 M solution of **2** in CH_2Cl_2 with trifluoroacetic acid (0.2 equiv.) at room temperature results in a first-order conversion (HPLC analysis) to an equilibrium mixture of **2** and **4** with a half-life of 3.1 hrs. Under identical conditions, **1** exhibits an epimerization half-life of approximately 20 days (GC analysis). Thus, the hydrazone epimerizes approximately 150 times faster than does the parent ketone. Although there have been a few reports of hydrazone epimerizations,[13a-c] *the ease with which this takes place relative to the corresponding ketone does not appear to have been recognized.* The hydrazone epimerization probably proceeds by reversable protonation of the C=N nitrogen and enamine formation. The ease of hydrazone epimerization relative to the parent ketone would be attributed to the greater basicity of nitrogen versus oxygen. Consistent with this, we observe that deuterium incorporation into acetone-tosylhydrazone (apparently both syn and anti) occurs ~200 times faster than for acetone itself (10 equiv. D_2O, 10 mol% TFA, THF-d_8, 25 °C). Also, rapid α-exchange of deuterium during tosylhydrazone formation has been observed.[14] In two cases, the formation of α-chiral tosylhydrazones under acid-free conditions apparently proceeded without epimerization,[13d,e] though this approach was unsuccessful in a cyclopentanone.[13b]

We also observe that the equilibrium ratio of hydrazones (71:29, cis:trans)[12b] is quite different from the equilibrium ratio of the corresponding ketones (~ 40:60, cis:trans).[15] Most notable here is the predominance of hydrazone **4**, which must have at least one substituent (either methyl or isopropyl) oriented axially on the somewhat flattened cyclohexane ring. Interestingly, the crystalline form of **4** exhibits an axial isopropyl group.[9] The preference for axial alkyl groups α to an exocyclic C=N of Z configuration (i.e., with the NHTs group syn to the α-substituent) has been attributed to relief of allylic strain,[16] though it is less clear why this should be so in the case of an E configuration such as found in **4**.

The conversion of the trans hydrazone **2** to the vinyl lithium **3** using an excess (5 equiv.)[3] of ^{n}BuLi•TMEDA occurs without epimerization, as evidenced by trapping of **3** with iodine and analysis of the resulting vinyl iodide

5. Thus, trans hydrazone 2 of ≥96% diastereomeric purity (by HPLC) was converted to trans iodide 5 of ≥99% diastereomeric purity (by GC) in 65% yield after distillation. Since vinyl iodides are excellent precursors to vinyllithium reagents, this process cleanly provides 3 in diastereomerically and enantiomerically pure form.

Menthonetosylhydrazone (2). Tosylhydrazine (32.00 g, 171.8 mmol) was suspended in acid-free dichloromethane (100 mL) and cooled to 0°C. To this stirred suspension was added (-)-menthone (40.0 mL mL, 231.6 mmol; trans:cis = 97:3) and the mixture was allowed to stir at 0 °C for 2 hours. After the addition of additional dichloromethane (50 mL), the mixture became nearly homogeneous and was then quickly passed through a 3-cm layer of silica gel on a coarse porosity fritted funnel, rinsing with two 20-mL portions of cold (≤ 0 °C) dichloromethane. The resultant clear, slightly yellow solution was immediately concentrated by rotary evaporation below room temperature. When the volume had been reduced by about half, hexanes (100 mL) were added and rotary evaporation continued. A white solid eventually formed and evaporation was continued until a dry solid resulted. This material was suspended in hexanes (150 mL) and transferred to a fritted glass funnel and washed with hexanes (3 x 50 mL). Drying under vacuum (0.1 mm Hg) yielded the *trans* hydrazone 2 (50.44 g, 91% yield) as a white powder (m.p. = 121-122°C). Diastereomeric purity was 97±1% by reversed-phase (C-18) HPLC (retention times: 2, 11.1 min; 4, 10.2 min.; gradient: 80% methanol/H_2O to 100% methanol over 10 minutes. Flow rate = 1 mL/min). $[\alpha]_D$ = - 75 ± 1° (c = 1, $CHCl_3$). IR (KBr): 3221 cm^{-1} (NH), 1642 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): 0.75 (d, 3H, J = 6.8); 0.78 (d, 3H, J = 6.7); 0.90 (d, 3H, J = 6.5); 1.04-1.15 (m, 1H); 1.18-1.30 (m, 1H); 1.51 (dd, 1H, J = 13.5, 10.7); 1.57-1.68 (m, 1H); 1.72-1.88 (m, 3H); 2.10 (octet, 1H, J = 6.7); 2.42 (s, 3H); 2.53 (ddd, 1H, J = 13.5, 3.9, 1.4); 7.29 (d, 2H, J = 8); 7.68 (br. s, 1H), 7.85 (d, 2H, J = 8). ^{13}C NMR ($CDCl_3$): 18.7, 21.3, 21.41, 21.47, 26.4, 27.1, 32.86, 32.93, 34.6, 50.4, 128.2, 129.3, 135.6, 143.6, 162.2. Calc for $C_{17}H_{26}N_2O_2S$: C 63.32, H 8.13, N 8.69, S 9.94; Found: C 63.27, H 8.13, N 8.74, S 9.96.

***trans*-1-Menthenyl iodide (5).** Hydrazone 2 (30.00 g, 93.1 mmol) was suspended in a mixture of hexanes (200 mL) and dry TMEDA (75 mL) and treated (at -78 °C) with n-butyllithium (10 M in hexanes; 46.5 mL, 465 mmol) over a 10-minute period. The deep red mixture was warmed (with gas evolution occurring at about 0 °C) to room temperature and held there for 1 hour. Then this solution was slowly transferred by cannula to a mechanically-stirred mixture of iodine (94.5 g, 372 mmol) and THF (300 mL) which had been cooled to -78 °C. The resulting dark brown suspension was brought to room temperature. Most of the THF was removed by rotary evaporation, then the organic phase was separated after addition of water (200 mL) and hexanes (100 mL). The aqueous phase was re-extracted once with hexanes (100 mL). The combined organic phases were washed with three 100-mL portions of water, followed by saturated NaCl solution (100 mL), and dried over Na_2SO_4. Rotary evaporation gave an orange oil, which was purified by vacuum distillation, yielding 5 (16.5 g, 65% yield), as a slightly yellow liquid, bp = 57-59 °C (0.12 mmHg), d = 1.37 g/cc. This material was 97.5% pure by capillary GC analysis (and contained only 0.8% of iodide 6). $[\alpha]_D$ = - 52 ± 1° (c = 1, $CHCl_3$). IR (neat): 1618 cm^{-1} (C=C). ^1H NMR ($CDCl_3$): 0.72 (d, 3H, J = 6.7); 0.94 (d, 3H, J = 6.8); 0.96 (d, 3H, J = 7); 1.12-1.25 (m, 1H); 1.43-1.56 (m, 1H); 1.64-1.73 (m, 1H); 1.79-1.88 (m, 1H); 2.15-2.34 (m, 3H); 6.36 (td, 1H, J = 2.1, 1.2). ^{13}C NMR ($CDCl_3$): 15.0, 20.3, 21.3, 22.8, 30.8, 32.2, 35.5, 48.6, 108.8, 146.4. HRMS (M^+) Calcd for $C_{10}H_{17}I$: 264.0375, found: 264.0380.

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