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Syntheses of Novel Chiral 2,5-Dialkyl-7-azabicyclo[2.2.1]heptanes and 2,5-Dialkyl-7-thiobicyclo[2.2.1]heptanes

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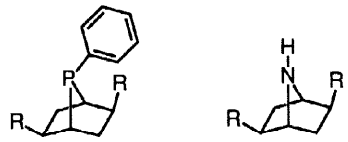
Abstract: New C_2-symmetric chiral amines with a rigid bicyclic framework have been synthesized *via* hydrogenation of monoazides catalyzed by 5% Pd/C in methanol. Enantiomerically pure 2,5-dialkyl-7-thiobicyclo[2.2.1]heptanes were made from readily available materials.

The design and synthesis of structurally novel chiral motifs play a crucial role in organic stereochemistry. C_2-symmetric chiral amines have been used widely as chiral auxiliaries in asymmetric synthesis.[1] These extensive studies have resulted in the application of many chiral amines.[2] Among these amines, the C_2-symmetric chiral pyrrolidine made first by Whitesell in 1977[2a] has been applied in a variety of asymmetric reactions.[3]

Recently, we reported the syntheses of novel chiral phosphabicyclo[2.2.1]heptanes **1** which were useful ligands in asymmetric palladium-catalyzed allylic alkylation[4] or catalysts in phosphine-mediated asymmetric [3+2] cycloaddition reactions (Figure 1).[5] Furthermore, we demonstrated that chiral phosphabicyclo[2.2.1]heptanes are more effective than the C_2-symmetric phospholanes - the phosphine analog of pyrrolidines, in the asymmetric [3+2] cycloaddition reaction. These results prompted us to explore the synthesis of the analogous chiral amines - azabicyclo[2.2.1]heptanes (**2**) (abbreviated ABH, Figure 1). We expect that the chiral azabicyclo[2.2.1]heptanes will be useful for many enantioselective reactions.



(1) (2)

R= Me, ^{i}Pr, etc. Figure 1

Compared with Whitesell's pyrrolidines, azabicyclo[2.2.1]heptanes **2** have a rigid fused bicyclic framework which limits the conformationally flexibility associated with the embedded five-membered ring. This feature may be important for some enantioselective reactions.

The synthesis of chiral azabicyclo[2.2.1]heptanes **2** relies on the availability of chiral 1,4 - diols **3** (Scheme 1) which are made readily from *p*-xylene and *p*-diisopropylbenzene according to Halterman's

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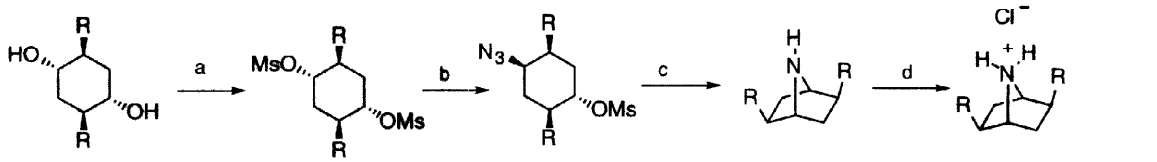
procedure[6] (the synthesis involves Birch reduction, asymmetric hydroboration and recrystallization). The chiral diols **3** can be converted into the bismesylates **4** in high yields (>99 %). Interestingly, the chiral amines **2** can not be made *via* nucleophilic substitution on the bismesylates **4**. This observation was unexpected based on similar transformations performed in the synthesis of other C_2 chiral amines.



3a R = Me **4a** R = Me **5a** R = Me, 49% **2a** R = Me **6a** R = Me (68 %)

3b R = ^{i}Pr **4b** R = ^{i}Pr **5b** R = ^{i}Pr, 47 % **2b** R = ^{i}Pr **6b** R = ^{i}Pr (73 %)

a., Et_3N, MsCl, CH_2Cl_2, 0 °C; b, NaN_3, DMF, 55 °C, 24 h; c, H_2, Pd/C (5%) in MeOH; d, HCl (g).

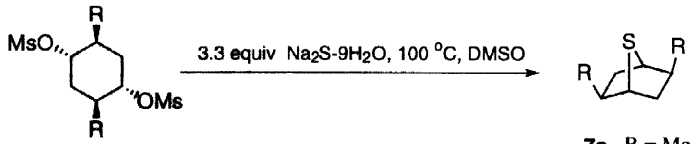
Scheme 1

A key step in the reaction is the nucleophilic attack of N_3^- on the bismesylates **4a/b** in DMF at 55 °C, which leads the formation of the monoazides **5a/b**, respectively, as the major products. Even in the presence of excess NaN_3 (e.g., 2 equiv), monoazides **5a/b** are still the major products. This is probably because axial nucleophilic attack by the second equiv of N_3^- is impeded by the disposition of the adjacent methyl group. LiN_3 can be used in place of NaN_3, and monoazides **5a/b** are formed in slightly higher yields as competing E_2 elimination is suppressed.

Synthesis of the bicyclo[2.2.1]framework continues with hydrogenation of monoazides **5a/b** using 5% Pd/C catalyst in methanol, followed by *in situ* nucleophilic attack of the derived primary amine on the mesylates. The yield depends on the work-up procedure. Since the chiral amines **2a/b** are water soluble, a useful synthetic route involves anhydrous operations and conversion of the chiral amines **2a/b** to the corresponding salts **6a/b**.[7]

Following is a typical procedure. Sodium azide (6.80 g, 105 mmol) and 2,5-dimethylcyclohexane-1,4-diol bis(methanesulfonate) (**4a**, 30.0 g, 100 mmol) in DMF (500 mL) was heated at 55 °C for 12h. The solution was then cooled to rt, followed by addition of water (200 mL). Ether (3 x 200 mL) was used to extract the product. The combined ether solution was washed with sat. aqueous NH_4Cl (3 x 100 mL), dried over sodium sulfate, and evaporated under *vacuo*. The residue was subjected to silica gel column chromatography, eluted with acetone/hexanes (1:10) to give the monoazide (**5a**, 12.1 g, 49 %). To monoazide (**5a**, 1.26 g, 5.1 mmol) in methanol (50 mL) was added 5% Pd/C (0.12 g). The solution was stirred at rt under H_2 for 2 days. After evaporation of MeOH, ether (25 mL) was used to dissolve the product and the solution was dried over NaOH (10 g). The NaOH residue was filtered and the filtrate was saturated with HCl gas. The precipitate was filtered and washed with ether (20 mL) to give the chiral amine·HCl (**6a**, 0.55 g, 68 %).

In related work, we have made the enantiomerically pure sulfides, 2,5-dialkyl-7-thiobicyclo[2.2.1]heptanes (abbreviated TBH), which may be useful for the asymmetric synthesis of chiral epoxides[8] (Scheme 2).



4a R = Me

4b R = ^{i}Pr

7a R = Me, 88%

7b R = ^{i}Pr, 72 %

Scheme 2

Nucleophilic addition of sodium sulfide nonahydrate in DMSO[9] to these mesylates afforded the desired sulfides **7a** and **7b** in respectable yields.[10] An elimination-aromatization product, 1,4-diisopropyl benzene, found in the synthesis of **7b**, could be removed by column chromatography. However, no *p*-xylene has been detected in the synthesis of **7a**.

A typical procedure is as follows: Sodium sulfide nonahydrate (24.0 g, 100 mmol) in DMSO (200 mL) was heated under vacuum (30 mmHg) until 35 mL of distillate was collected. After cooling to 40 °C, 2,5-dimethylcyclohexane-1,4-diol bis(methanesulfonate) (**4a**, 9.0 g, 30 mmol) was added and the resulting mixture was heated at 100 °C for 20 h. The solution was then cooled to rt, followed by addition of ice water (200 mL). Pentane (3 x 100 mL) was used to extract the product. The combined pentane solution was washed with water (3 x 20 mL) , dried over sodium sulfate, and evaporated under reduced pressure. The high boiling residue was subjected to bulb-to-bulb distillation giving product **7a** (3.8 g, 88% yield).

Asymmetric reactions based on these interesting chiral azabicyclo[2.2.1]heptanes and thiobicyclo[2.2.1]heptanes are currently being explored in our lab and experimental results will be reported in due course.

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7. The spectra of monoazides (**5**) and chiral amines (**6**)·HCl: (**5a**) ^{1}H NMR ($CDCl_3$): δ 4.52-4.44 (m, 1H), 3.70-3.60 (m, 1H), 3.00 (s, 3H), 2.30-2.20 (m, 1H), 2.10-2.00 (m, 1H), 1.92-1.68 (m, 3H), 1.58-1.49 (m, 1H), 1.10 (d, 3H), 1.00 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 82.4, 61.3, 38.6, 35.8, 35.6, 31.9, 18.2, 13.5. (**5b**) ^{1}H NMR ($CDCl_3$): δ 5.08-5.02 (m, 1H), 3.95-3.90 (m, 1H), 3.00 (s, 3H), 2.15-2.05 (m, 1H), 2.05-1.85 (m, 3H), 1.68-1.50 (m, 4H), 1.05-0.85 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 80.9, 59.9, 45.0, 41.0, 38.7, 28.6, 28.1, 27.1, 26.1, 21.0, 20.7, 20.6. (**6a**) 2,5-Dimethyl-7-azabicyclo[2,2,1]heptane•HCl: ^{1}H NMR ($CDCl_3$): δ 9.60-9.40 (b, 2H), 3.82 (d, J = 4.35 Hz, 2H), 1.97-1.83 (m, 4H), 1.72-1.65 (m, 2H), 1.26 (d, J = 6.82 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 64.7, 36.9, 34.6, 19.9. MS (m/z) 161, 125 (M^+-HCl, 9), 110 (8), 83 (49), 82 (35), 68 (93), 36 (100). (**6b**) 2,5-Diisopropyl-7-azabicyclo[2,2,1]heptane•HCl: ^{1}H NMR ($CDCl_3$): δ 9.45-9.25 (b, 2H), 4.07 (d, J = 4.16 Hz, 2H), 1.95-1.70 (m, 6H), 1.40-1.30 (m, 2H), 0.97 (d, J = 6.41 Hz, 6H), 0.82-0.80 (d, J = 6.48 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 60.8, 48.5, 35.0, 30.9, 22.1, 19.8. MS (m/z) 217, 181(M^+-HCl, 2), 166 (4), 138 (26), 111 (15), 95 (2), 81 (4), 69 (11), 68 (100), 55 (6).
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10. Both sulfides **7a** and **7b** are noxious, routine workup (e.g., extraction with pentane, removal of the solvent and further purification bulb-to-bulb distillation or column chromatography) should be manipulated in a hood. Spectra data for **7a**: ^{1}H-NMR ($CDCl_3$) δ 0.94 (d, J = 6.3 Hz, 3H), 1.19 (dd, J = 6.3, 4.0 Hz, 1H), 1.70~1.80 (m, 2H), 3.35 (d, J = 4.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 21.97, 38.04, 43.00, 59.58; HRMS Calcd for $C_8H_{12}S$: 142.0816; found: 142.0805. **7b**: ^{1}H-NMR ($CDCl_3$) δ 0.79 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H), 1.10~1.25(m, 1H), 1.26~1.43 (m, 2H), 1.60~1.70 (m, 1H), 3.66 (d, J = 2.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 19.81, 21.56, 32.66, 41.03, 52.31, 55.04; HRMS Calcd for $C_{12}H_{20}S$: 198.1442; found: 198.1425.