Diastereoselective Cyclopentane Construction

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Received December 6, 1999

In the course of other work,[1] we have observed that reduction of the tosylhydrazone of ketone **2** (Scheme 1) with $NaBH_3CN$ gave efficient cyclization to the cyclopentanes **3** and **4**, with high selectivity for the cis-dialkyl product **3**.

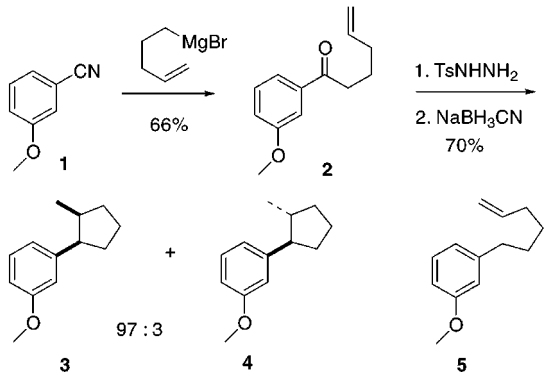
We prepared ketone **2** by condensation of the nitrile **1** with the Grignard reagent prepared from 5-bromopentene. Reduction was carried out by the method of Kim.[2] We observed efficient cyclization (70%), with the dominant cyclized product having a methyl doublet at δ 0.59, and the minor cyclized product having a methyl doublet at δ 0.92. In a closely related system,[3] the cis diastereomer had a chemical shift of δ 0.69, and the trans diastereomer had a methyl doublet at δ 0.93. We also isolated a 29% yield of the reduced but not cyclized product **5** from the reaction.

We had thought[1] that these cyclizations were proceeding by a free-radical mechanism. Thus (Scheme 2), reduction of the tosylhydrazone would give the monoalkyl diazene **6**. Hydrogen atom abstraction would give **7**, which would lose nitrogen to give the alkyl radical **8**. The intermediate radical **8** could either accept a hydrogen atom from **6** to give the uncyclized product **5**, or cyclize to a mixture of **9** and **10**, which would accept hydrogen atoms to become **3** and **4**. This mechanism was supported by parallel work that had been reported by Myers.[4]

This view of the mechanism suggested that a higher concentration of reactants should favor the open chain product **5**, while a lower concentration of reactants should favor the cyclized products **2** and **3**. In a brief study (Table 1) we found this to be the case.

With these results in hand, we carried out the cyclization under more conventional free radical conditions. To this end we prepared (Scheme 3) the alcohol **12**. The derived imidazole thiocarbamate **13** was contaminated with 10% of the alkene **14**, but was too unstable to purify, so we immediately submitted it to reduction with Bu_3SnH in refluxing benzene. This gave **3** and **4** as before, but now in a 29:71 cis-to-trans ratio, and in 39% yield. As before, the major side product was the reduced but not cyclized alkene **5** (39% yield). This was accompanied by a 10% yield of the elimination product **14**, from dehydration of **12** in the course of thiocarbamylation. An additional minor component, observed at δ 42 in the ^{13}C NMR spectrum of the mixture of **3** and **4**, was assigned

Scheme 1



Scheme 2

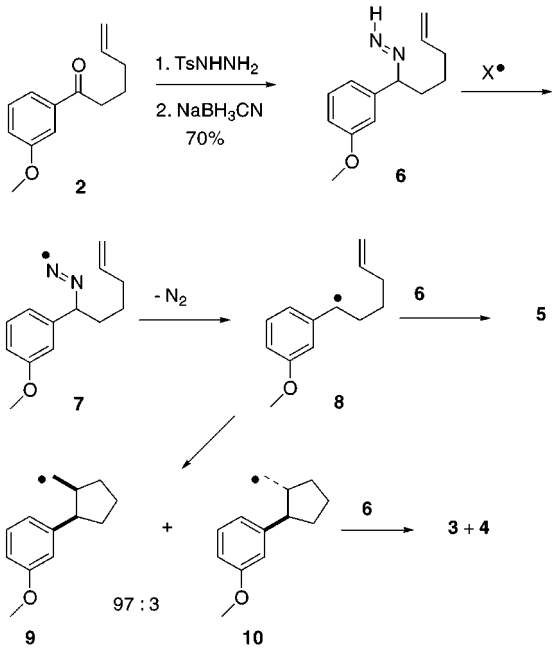
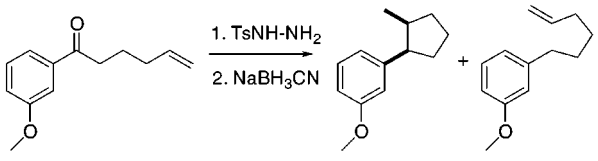


Table 1. Effect of Concentration on the Cyclization of Ketone 2



Entry	Concentration of 1 (M)	Ratio (3+4 : 5)
1	.27	50:50
2	.034	71:29
3	.0084	77:23

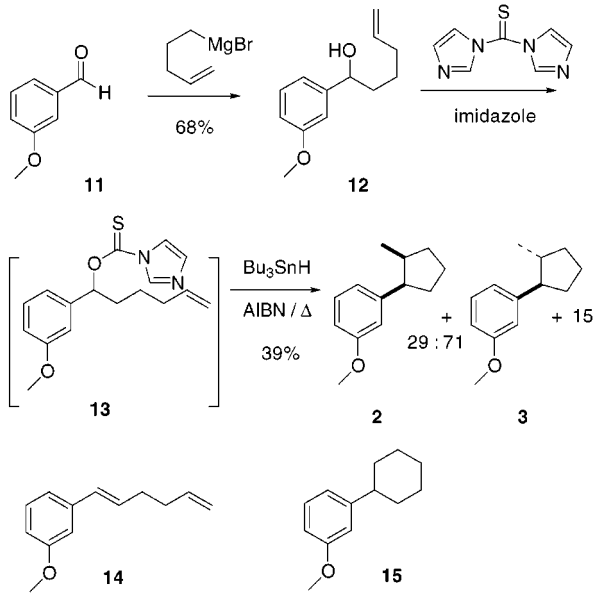
the structure **15**.[5] We did not observe **15** in the mixture of **3** and **4** from the reduction of the tosylhydrazone of **2.**

We hypothesize (Scheme 4) that with Bu_3SnH, the radical was at least partially equilibrating between the

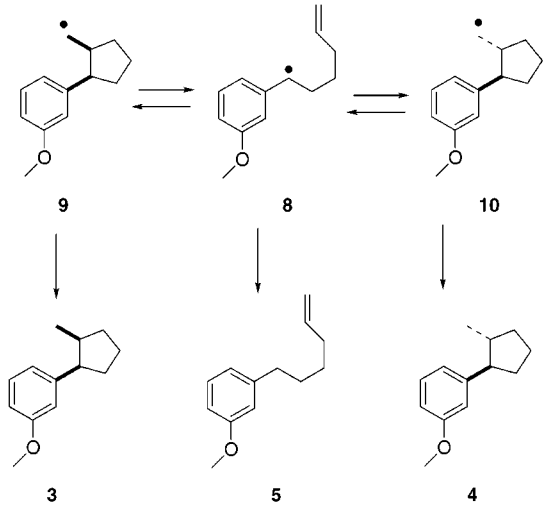
(1) Taber, D. F.; Wang, Y.; Stachel, S. J. *Tetrahedron Lett.* **1993**, *34*, 6209.
(2) Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927.
(3) Taber, D. F.; Anthony, J. M. *Tetrahedron Lett.* **1980**, *21*, 2779.
(4) (a) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572. (b) Myers, A. G.; Movassaghi, M.; Zheng, B. *Tetrahedron Lett.* **1997**, *38*, 6569.
(5) Walling reported that phenylcyclohexane is eventually produced under conditions of slow H-atom transfer: Walling, C.; Cioffari, A. *J. Am. Chem.* **1972**, *94*, 6064.

10.1021/jo991866u CCC: $19.00
Published on Web 05/19/2000

Scheme 3



Scheme 4



open **8** and the two cyclized diastereomers **9** and **10**. The concentrations of each of these, and the relative rates of H-atom transfer to each, then determined the final product ratio.[6] With the tosylhydrazone reduction, on the other hand, the hydrogen atom donor was the much faster monoalkyl diazene.[7] In this case, the competition was between direct H-atom transfer to the benzylic radical **8**, and cyclization. The cyclized radical then accepted an H-atom before appreciable retrocyclization and equilibration could occur.[8,9]

We expect that the high diastereoselectivity that we have observed for the cyclization of **2** will be generally true for the cyclization of aryl ketones, thus establishing a reliable approach to the family of thermodynamically less stable cis 1,2-dialkylcyclopentane derivatives.

Experimental Section

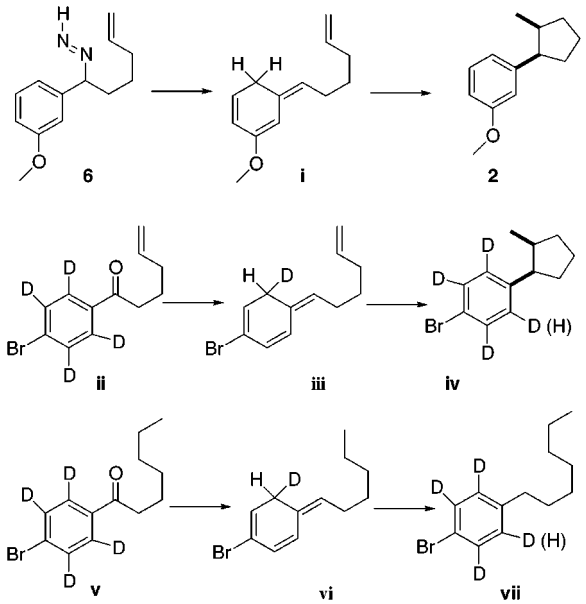
General. ^{1}H NMR (at 300 MHz) and ^{13}C NMR (at 75 MHz) spectra were obtained as solutions in deuteriochloroform ($CDCl_3$). The infrared (IR) spectra were determined as solutions in CCl_4 in a 1 cm KBr solution cell using a FTIR. R_f values indicated refer to thin-layer chromatography (TLC) on 5.0 × 10 cm, 250 μm analytical plates coated with silica gel 60 F_{254}, developed in the solvent system indicated. Elemental analysis was carried out by Quantitative Technologies Inc., P.O. Box 470, Salem Industrial Park, Bldg 5, Whitehouse, NJ 08888. Column chromatography was carried out following the procedure described by Taber[10] using silica gel 60 particle size 0.040−0.063 μm. The solvent mixtures used are volume/volume mixtures. All glassware was dried in a vacuum oven and all reactions were carried out under a flow of dry nitrogen. Tetrahydrofuran (THF) and diethyl ether were from Aldrich Sure/Seal bottles, kept under dry nitrogen. All reaction mixtures were stirred magnetically, unless otherwise noted.

1-(3-Methoxyphenyl)-5-hexenone (2). To a 1-L three-neck round-bottom flask, 5-bromo-1-pentene (25.0 g, 0.17 mol) in anhydrous ether (50 mL) was added dropwise to magnesium turnings (5.2 g, 0.21 mol) in anhydrous ether (125 mL), over 15 min at gentle reflux. After 1 h, the reaction was allowed to cool to room temperature, and 3-methoxybenzonitrile (20.3 g, 0.153 mol) in anhydrous ether (100 mL) was added over 15 min. After 13 h at reflux, the reaction mixture was cooled to 0 °C and then partitioned between Et_2O and sequentially, 1 N aqueous HCl and saturated aqueous NaCl. The combined organic extracts were dried ($MgSO_4$) and concentrated to leave **2** as a clear oil (20.6 g, 66% yield). ^{1}H NMR δ 7.54−7.51 (d, J = 8.1 Hz, 1H), 7.48 (s, 1H), 7.36 (t, J = 8.1 Hz, 1H), 7.11−7.08 (d, J = 8.1 Hz, 1H), 5.83 (ddt, J = 17.1, 9.9, 6.9 Hz, 1H), 5.02 (d, J = 17.1 Hz,

(6) (a) This analysis is complicated by the many competing rate constants involved. It is relevant that Newcomb reported the H-atom transfer to a benzylic radical from Bu_3SnH is about 2 orders of magnitude slower than H-atom transfer to a terminal alkyl radical: Newcomb, M. *Tetrahedron* **1993**, *49*, 1151. (b) The reversibility of benzylic radical cyclization might help to rationalize the contrasting diastereoselectivity observed by Rawal: Chambournier, G.; Krishnamurthy, V. Rawal, V. H. *Tetrahedron Lett.* **1997**, *38*, 6313.

(7) Myers (ref 4b) concluded that H-atom transfer from a monoalkyl diazene is about 1 order of magnitude faster than H-atom transfer from Bu_3SnH.

(8) It was formally possible that the cyclization of the monoalkyl diazene might be proceeding via sequential sigmatropic rearrangements (**6** → **i** → **3**). To assess this alternative, we prepared and reduced the deuterated ketone **ii**. The cyclized product **iv** showed ∼15% incorporation of H (^{1}H NMR) at one ortho position. There was not enough of the reduced but not cyclized product to analyze, so we also prepared and reduced the ketone **v**. The product **vii** also showed ∼15% incorporation of H at one ortho position, so the cyclization is apparently not proceeding by a mechanism that would lead to significant aryl H−D exchange. It would be unusual if the kinetic isotope effects for the conversion of **iii** to **iv** and for the conversion of **vi** to **vii** were each ∼3.3.



(9) For each cyclization, the ratio of **3** to **4** was established by integration of the secondary methyl signals in the ^{1}H NMR spectrum of the mixture of the two.

(10) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

1 H), 5.00 (d, J = 9.9 Hz., 1H), 3.85 (s, 3H), 2.96 (t, J = 7.2 Hz, 2H), 2.15 (q, J = 7.2 Hz, 2H), 1.85 (m, 2H); ^{13}C NMR δ CH_3: 54.2 CH_2: 114.4, 36.5, 31.8, 21.9 CH: 137.3, 128.7, 119.8, 118.4, 111.4 C: 199.6, 159.2, 137.7; IR 2938, 1688, 1641, 1597, 1549, 1464 cm^{-1}; Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.24; H, 7.89. Found: C, 75.85; H, 7.87.

1-Methyl-2-(3-methoxyphenyl)cyclopentane 3 and 4, Predominantly 3. The ketone **2** (2.07 g, 10.1 mmol) was added to *p*-toluenesulfonyl hydrazide (2.08 g, 11.2 mmol) in anhydrous THF (20 mL) at reflux. After 16 h, the mixture was cooled to room temperature and then partitioned between water and EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated to give 3.73 g of a solid. Recrystallization of the solid from 1:1 hexanes/1-chlorobutane (30 mL) gave the tosylhydrazone as a white solid (3.69 g, 99% yield, mp = 97 °C). ^{1}H NMR δ 7.91 (d, J = 8.7 Hz, 2H), 7.88 (bs, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.17−7.28 (m, 3H), 6.89 (d, J = 7.0 Hz, 1H), 5.69−5.81 (ddt, J = 6.7, 16.7, 9.2 Hz, 1H), 5.03 (d, J = 9.2 Hz, 1H), 5.01 (d, J = 16.7 Hz, 1H), 3.82 (s, 3H), 2.53 (t, J = 7.9 Hz, 2H), 2.42 (s, 3H), 2.05 (q, J = 6.7 Hz, 2H), 1.56 (m, 2H); ^{13}C NMR δ CH_3: 54.0, 20.2, CH_2: 115.5, 31.8, 24.4, 23.4, CH: 134.6, 128.7, 128.5, 127.3, 118.0, 114.4, 110.9, C: 158.9, 154.8, 143.4, 136.9, 136.5; IR 3215, 1549, 1387 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2O_3S$: C, 64.31; H, 6.49; N, 7.52. Found: C, 63.94; H, 6.47; N, 7.57.

The tosylhydrazone (1.00 g, 2.70 mmol) was dissolved in anhydrous THF (10 mL). Zinc(II) chloride (446 mg, 3.7 mmol) was added followed by $NaBH_3CN$ (212 mg, 3.7 mmol). The reaction mixture was heated to reflux. After 18 h, the reaction mixture was cooled to room temperature and partitioned between EtOAc and sequentially, saturated aqueous $NaHCO_3$, 1 N aqueous HCl, and water. The organic extracts were dried ($MgSO_4$) and concentrated to a crude oil, which was purified by column chromatography, to give **3** and **4** as a colorless oil (257 mg, 70% yield). TLC R_f (hexanes) = 0.45. This oil was a 3:97 trans:cis isomeric mixture. ^{1}H NMR δ 7.18 (t, J = 8.1 Hz, 1H), 6.70−6.78 (m, 3H), 3.78 (s, 3H), 3.10 (q, J = 7.7 Hz, 1H), 2.23−2.34 (m, 1H), 1.81−1.99 (m, 4H), 1.61−1.76 (m, 1H), 1.32−1.43 (m, 1H), 0.91 (d, J = 6.9 Hz, 0.09H), 0.59 (d, J = 6.9 Hz, 2.91H); ^{13}C NMR δ (major) CH_3: 53.9, 14.8 CH_2: 32.1, 27.6, 21.9 CH: 127.9, 120.1, 113.7, 109.5, 48.0, 36.9 C: 158.7, 144.6; IR 2955, 2872, 1582, 1548 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.83; H, 9.30. This was followed by **5** (106 mg, 29% yield). TLC R_f (hexanes) = 0.42; ^{1}H NMR δ 7.19 (t, J = 7.5 Hz, 1H), 6.71−6.78 (m, 3H), 5.79 (ddt, J = 17.0, 10.3, 7.1 Hz, 1H), 4.99 (d, J = 17.0 Hz, 1H), 4.93 (d, J = 10.3 Hz, 1H), 3.79 (s, 3H), 2.59 (t, J = 7.5, 2H), 2.07 (q, J = 7.1, 2H), 1.63 (q, J = 6.8 Hz, 2H), 1.43 (q, J = 7.1, 2H); ^{13}C NMR δ CH_3: 53.6 CH_2: 112.9, 34.3, 32.1, 29.3, 27.0 CH: 137.3, 127.7, 119.3, 112.7, 109.3 C: 158.1, 142.8; IR 2934, 1584 cm^{-1}; Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.69; H, 9.28. This was followed by recovered ketone **2** (161 mg, 0.79 mmol).

1-(3-Methoxyphenyl)-5-hexenol (12). In a 1-L three-neck round-bottom flask, 5-bromo-1-pentene (25.0 g, 0.17 mol) in anhydrous ether (50 mL) was added dropwise to magnesium turnings (5.2 g, 0.21 mol) in anhydrous ether (300 mL), over 15 min at gentle reflux. After 1 h, 3-methoxybenzaldehyde **11** (20.8 g, 0.153 mol) in anhydrous ether (50 mL) was added dropwise to the reaction mixture over 15 min. After 2 h at gentle reflux, the reaction mixture was cooled to room temperature and partitioned between ether and saturated aqueous NH_4Cl. The combined organic extracts were dried ($MgSO_4$) and concentrated to a crude oil which was chromatographed, to give **12** as a colorless oil (21.4 g, 68% yield). TLC R_f (1:4 EtOAc:hexanes) = 0.40. ^{1}H NMR δ 7.25 (t, J = 8.1 Hz, 1 H), 6.89−6.91 (m, 2H), 6.81 (d, J = 8.1 Hz, 1H), 5.77 (ddt, J = 6.0, 17.1, 9.9 Hz, 1H), 4.98 (d, J = 17.1 Hz, 1H), 4.94 (d, J = 9.9 Hz, 1H), 4.63 (m, 1H), 3.80 (s, 3H), 2.07 (q, J = 6.0 Hz, 2H), 1.66−1.81 (m, 2H), 1.47−1.57 (m, 1H), 1.35−1.45 (m, 1H); ^{13}C NMR δ CH_3: 53.9 CH_2: 113.7, 37.1, 32.3, 23.7 CH: 137.9, 128.5, 117.4, 111.8, 110.5, 73.0 C: 159.0, 146.1; IR 3615, 2937, 1586 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.39; H, 8.80. Found: C, 74.98; H, 8.80.

1-Methyl-2-(3-methoxyphenyl)cyclopentane 3 and 4, Predominantly 4. 1-(3-Methoxyphenyl)-5-hexenol **12** (5.0 g, 0.024 mol) was added to CH_2Cl_2 (100 mL), followed by addition of 1,1′-thiocarbonyldiimidazole (4.8 g, 0.027 mol) and imidazole (3.7 g, 0.027 mol). The reaction mixture was then heated to reflux. After 1.5 h, the reaction mixture was partitioned between CH_2Cl_2, and, sequentially, cold 1 N aqueous HCl, saturated aqueous $NaHCO_3$, and water. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was taken up in benzene (1500 mL) and a catalytic amount of AIBN (0.150 g) was added. The reaction mixture was heated to reflux, and $HSnBu_3$ (7.8 g, 0.027 mol) in benzene (100 mL) was added over 1 h. After 24 h, the reaction mixture was cooled to room temperature, and the benzene was removed under reduced pressure to leave a crude oil, that was purified by column chromatography to give **3** and **4** as a colorless oil (1.8 g, 39% yield). TLC R_f (hexanes) = 0.45. This oil was a 71:27 trans:cis isomeric ratio. ^{1}H NMR δ 7.18−7.25 (m, 1H), 6.70−6.81 (m, 3H), 3.79 (s, 3H), 3.10 (q, J = 7.7 Hz, 0.3H), 2.21−2.43 (m, 1.7H), 1.63−2.09 (m, 4H), 1.23−1.42 (m, 2H), 0.91 (d, J = 6.9 Hz, 2.1H), 0.59 (d, J = 6.9 Hz, 0.7H); ^{13}C NMR δ (major) CH_3: 53.9, 17.2 CH_2: 34.0, 33.4, 22.5 CH: 128.3, 119.1, 112.6, 109.9, 53.4, 41.6 C: 158.9, 146.5; IR 2954, 2869, 1600, 1583, 1549, 1491, 1452, 1263, 1157, 1053 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H 9.53. Found: C, 82.14; H, 9.83. This was followed by a 4:1 mixture of **5** and **14** (2.3 g, 49% yield). TLC R_f (hexanes) = 0.43. For **14**: ^{1}H NMR δ 7.21 (t, J = 7.9 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.87 (s, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.38 (d, J = 15.8 Hz, 1H), 6.23 (dt, J = 15.8, 6.6 Hz, 1H), 5.85 (ddt, J = 18.8, 10.1, 6.5 Hz, 1H), 5.05 (d, J = 18.8 Hz, 1H), 4.99 (d, J = 10.1 Hz, 1H), 3.81 (s, 3H), 2.22−2.33 (m, 4H); ^{13}C NMR δ CH_3: 53.7 CH_2: 113.4, 32.0, 30.9 CH: 136.5, 129.0, 128.5, 127.9, 117.1, 110.9, 109.8 C: 158.2, 137.7; IR 2929, 1548 cm^{-1}.

Acknowledgment. We thank DuPont Agricultural Products for financial support. We also thank Dr. King Mo Sun and Dr. James A. Kerschen for many helpful comments and suggestions.

Supporting Information Available: Spectroscopic data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO991866U