suspension of potassium hydride (0.136 g, 3.39 mmol, 1.13 equiv) in dry DMF (3 mL) under an argon atmosphere was added bis(enol ether) **7b** (1.69 g, 3 mmol) in dry DMF (15 mL) at −20 °C. The solution was stirred for 1 h at −20 °C, after which it was cooled to −70 °C (dry ice/hexane) and methyl iodide (0.5 mL, 8.03 mmol) was added. The mixture was stirred for 3 h at −60 to −50 °C, after which the reaction mixture was allowed to warm to −30 °C and water (5 mL) was added, followed by dilute HCl (1 N, 50 mL). The mixture was extracted with $CHCl_3$ (3 × 50 mL), and the combined layers were washed with H_2O (2 × 50 mL), brine and dried ($MgSO_4$). Removal of solvent under reduced pressure gave 1.45 g (82%) of an oily product, which was used directly for hydrolysis.

General Procedure for the Hydrolysis of 8. Method A. Decarboxylation was effected by heating the alkylated material **8** (2.5 mmol) in a mixture of glacial acetic acid (15 mL) and aqueous HCl (15 mL, 1 N) at reflux. After being heated for 2 h, the reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with aqueous $NaHCO_3$ solution (10% w/w) and dried ($MgSO_4$). The solvent was removed under water aspirator pressure to provide an oil, which was further purified by column chromatography over silica gel (20:80 ethyl acetate/hexane) to give pure **9**.

Method B.[18] The alkylated material **8** (2 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with trifluoroacetic acid (7 mL) at room temperature for 1 h. The solvent was removed under reduced pressure to provide an oil, which was dissolved in dioxane (30 mL), treated with aqueous HCl (7.5 mL, 1 N), and then heated at reflux for 2.5 days. The reaction mixture was cooled, concentrated under reduced pressure, diluted with water (20 mL), and extracted with $CHCl_3$ (3 × 50 mL). The organic layers were combined, washed with aqueous $NaHCO_3$ (10% w/w) solution, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give an oil, which was further purified by column chromatography (silica gel, 15 g) to give pure monoalkylated *cis*-bicyclo[3.3.0]octane-3,7-dione **9**.

2-Methyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (9a). This material was obtained as a mixture of epimeric isomers at position 2: IR (neat) 2930, 1735, 1140 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05, and 1.15 (3 H, 2 s), 1.70–2.10 (2 H, m), 2.20–2.80 (5 H, m), 2.90–3.20 (2 H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) major isomer δ 219.0, 217.9, 48.01, 44.85, 43.47, 43.40, 43.04, 33.95, 13.21; mass spectrum (CI, CH_4), *m/e* 153 (M + 1, 100); high-resolution mass spectrum calcd for $C_9H_{12}O_2$ 152.0837, found 152.0836.

2-Ethyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (9b). This material was obtained as a mixture of epimeric isomers at position 2: IR (neat) 2950, 1730, 1400, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80–1.00 (3 H, m), 1.40–3.20 (11H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) major isomer δ 219.25, 218.00, 54.40, 44.23, 43.74, 43.61, 42.28, 34.40, 22.69, 11.50; mass spectrum (CI, CH_4) *m/e* 167 (M + 1, 100); high-resolution mass spectrum calcd for $C_{10}H_{14}O_2$ 166.0993, found 166.0997.

2-Allyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (9c). This material was obtained as a mixture of epimeric isomers at position **2**: IR (neat) 2920, 1725, 1630, 1140, 900 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.90–2.80 (9 H, m), 2.90–3.20 (2 H, m), 4.90–5.10 (2 H, m), 5.70–5.90 (1 H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) major isomer δ 218.10, 217.65, 134.66, 117. 33, 52.41, 43.69, 43.30, 41.73, 34.01, 33.49; mass spectrum (CI, CH_4), *m/e* 179 (M + 1, 100), 137 (9.1). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.15; H, 7.86. Found: C, 74.19; H, 7.86.

2-Propargyl-*cis*-bicyclo[3.3.0]octane-3,7-dione (9d). This material was obtained as a mixture of epimeric isomers at position 2: IR (neat) 3300, 1740, 1400, 1140 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70–2.20 (2 H, m), 2.30–2.90 (8 H, m), 2.95–3.20 (2 H, m); ^{13}C NMR (62.8 MHz, $CDCl_3$) major isomer δ 217.63, 216.59, 80.59, 70.34, 50.86, 43.84, 43.23, 41.87, 34.12, 17.95; mass spectrum (CI, CH_4), *m/e* 177 (M + 1, 100); high-resolution mass spectrum calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0835.

Acknowledgment. We wish to thank the NSF (Grant CHE-8604443) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous support of this research. The technical skills of Anju Gupta in the preparation of this manuscript are also gratefully acknowledged.

(18) Anwer, M.; Spatola, A. F. *Synthesis* **1980**, 929.

The Inverse Electron Demand Diels–Alder Reaction of 3-(Methylsulfonyl)-1,2,4-triazine and Enamines: Isolation of Crystalline Intermediates and an Improved Synthesis of 1-(Methylsulfonyl)tetrahydroisoquinolines

B. L. Chenard* and R. T. Ronau

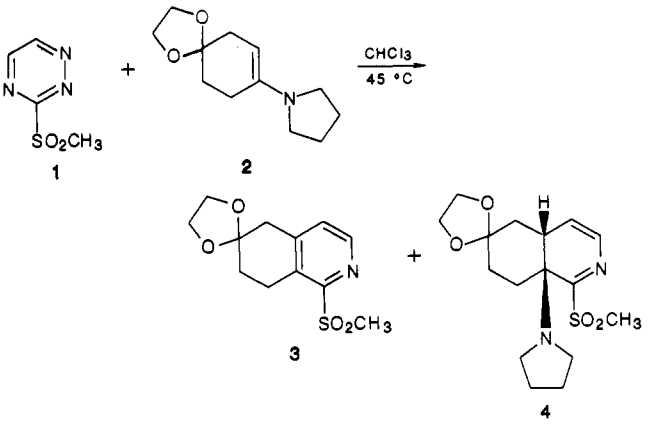
Central Research, Pfizer Inc., Groton, Connecticut 06340

Gayle K. Schulte[1]

Chemical Instrumentation Center, Yale University, New Haven, Connecticut 06511

Received April 26, 1988

In connection with other work, we required tetrahydroisoquinolines and pursued these targets with the inverse electron demand Diels–Alder reaction of 1,2,4-triazines and enamines, a process that has been developed by Boger[2] and more recently by Taylor.[3] Although the procedure works well for acyclic and cyclopentyl enamines, it has been reported to give only poor yields with cyclohexyl enamines.[4] Therefore it was not surprising that when we reacted triazine **1**[3] and **2** under the standard conditions (chloroform, 45 °C) a miserable yield of tetrahydroisoquinoline **3** (15%) was obtained. In addition to **3**, we also obtained another crystalline product, which we tentatively identified as **4** (20%) on the basis of its NMR spectrum and elemental analysis.

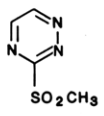
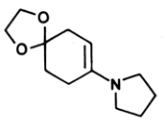
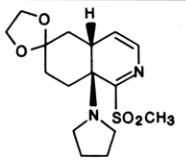
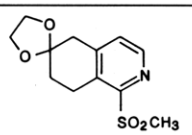
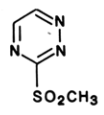
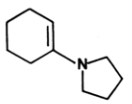
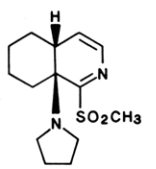
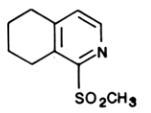
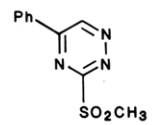
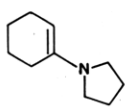
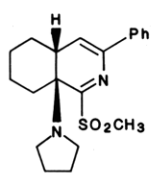
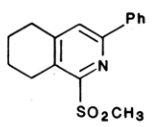


There have been three reports[5] implicating structures such as **4** as intermediates in triazine cycloadditions, but none give any spectral or analytical data to support the structure. Also, the stereochemistry of **4** could have some mechanistic implications regarding the inverse electron

(1) Address inquires regarding the X-ray structure determination to this author.
(2) For a review see: Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
(3) Taylor, E. C.; Pont, J. L.; Warner, J. C. *Tetrahedron* **1987**, *43*, 5159. Taylor, E. C.; Macor, J. E. *Tetrahedron Lett.* **1985**, *26*, 2415.
(4) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179.
(5) Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem.* **1982**, *47*, 895. Dittmar, W.; Sauer, J.; Steigel, A. *Tetrahedron Lett.* **1969**, 5171. Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1987**, *52*, 4280.

0022-3263/88/1953-5175$01.50/0

Table I. Stepwise Synthesis of Dihydropyridines and Pyridines

triazine	enamine	dihydropyridine (%)	tetrahydroisoquinoline (%)
 1	 2	 4 (70%)	 3 (76%)
 1		 5 (65%)	 7 (81%)
		 6 (78%)	 8 (70%)

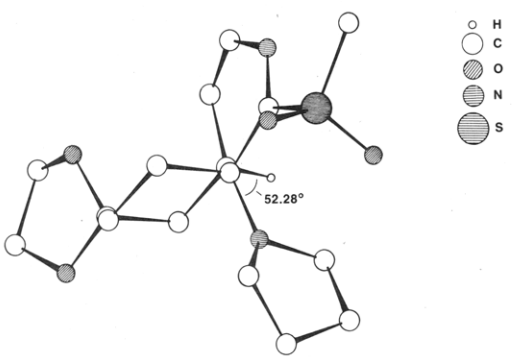


Figure 1. X-ray structure of **4**.

demand Diels–Alder reaction. For these reasons and to gain a better understanding of the problems involved in the aromatization step, we obtained an X-ray analysis. As is plainly visible in Figure 1, the adduct possesses a cis fused ring junction. This structure supports a concerted pathway, although it is far from conclusive evidence. More importantly, the torsion angle between the bridging hydrogen and nitrogen atoms (52.28°) is particularly poorly aligned for E_2 elimination,[6] accounting for the exceptional stability of **4** compared to its cyclopentyl, cycloheptyl, and acyclic counterparts.

It has been suggested that the addition of acetic acid to the reaction may improve the overall process.[7] In fact when **1** and **2** were combined in methylene chloride with 1 equiv of acetic acid, **3** was the only isolable product (10%). In light of the poor conversion to **3**, we chose to optimize the yield of the dihydropyridine and subsequently eliminate pyrrolidine in a separate step.

When **1** and **2** were combined in dry methylene chloride at 0 °C, immediate nitrogen evolution was observed. If the solvent was removed immediately upon cessation of bubbling, a 70% yield of **4** could be obtained after trituration with ether–hexanes. It was essential that the dihydropyridine be isolated promptly as it showed a marked propensity to decompose in the reaction medium. Unfortunately aromatization to the tetrahydroisoquinoline was only a minor pathway for the decomposition. Crystalline dihydropyridines could also be isolated from other cyclization reactions by using these mild reaction conditions. Thus **5** and **6** were obtained as bright yellow solids (65% and 78%, respectively, see Table I).

With the dihydropyridines now readily accessible, attention was turned to improving the elimination step.[8] Our approach was to take advantage of the cis fusion by effecting elimination through a cyclic process. If we could selectively oxidize the pyrrolidine nitrogen, a Cope elimination should produce the desired products.[9] *m*-Chloroperoxybenzoic acid (MCPBA) effected this selective oxidation at ambient temperature. Not surprisingly these *N*-oxides spontaneously decomposed with loss of *N*-hydroxypyrrolidine to give the desired pyridines in 70–80% isolated yield (Table I).

With both steps of the tetrahydroisoquinoline synthesis now efficient, we attempted to perform the overall sequence in one pot. Thus **1** and 1-pyrrolidinylcyclohexene were combined at 0 °C and allowed to warm to ambient temperature. When nitrogen evolution ceased, MCPBA (3 equiv)[10] was added directly to the reaction mixture. After 3 h at ambient temperature, the reaction was complete and **7** was isolated by silica gel flash chromatography.

(6) E_2 elimination reactions generally occur with the leaving groups antiperiplanar (180° torsion angle). When this is not possible, elimination can still occur through a 0° torsion angle but the elimination is slower. Elimination with the cis orientation is generally acceptable in cyclopentanes but can be as much as 10000 times slower for comparable cyclohexane eliminations. See: Alder, R. W.; Baker, R.; Brown, J. M. *Mechanism in Organic Chemistry*; Wiley Interscience: New York, 1971; pp 220–227.

(7) Taylor, E. C.; Macor, J. E., manuscript submitted to *J. Org. Chem.* We thank the authors for a preprint of this work.

(8) Boger had previously attempted to accomplish this same task by the addition of protic acid, Lewis acid, and heat to the initial Diels–Alder reaction. All of these modifications would favor an E_1 process and were uniformly unsuccessful. See ref 4.

(9) For a review, see: DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431.

(10) Three equivalents of MCPBA are necessary for complete conversion to the tetrahydroisoquinoline. Overoxidation does not appear to be the problem in this reaction as the tetrahydroisoquinolines have been shown to be stable to MCPBA for at least 24 h under these conditions.

Unfortunately, the yield for the one-pot process was only 38%. As stated above, this seems to be due to the instability of the dihydropyridines in the reaction medium. Once isolated, they are quite stable as solids, in methylene chloride solution at ambient temperature, and to silica gel chromatography.

In summary, we have found that 1-(methylsulfonyl)-5,6,7,8-tetrahydroisoquinolines may be prepared in good overall yield by a simple two-step process. This procedure may prove to be a general route to tetrahydroisoquinolines.[11] The intermediate dihydropyridines have been isolated and well characterized.

Experimental Section

General Procedures. Melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 283B or 1420 spectrophotometers in chloroform solution and are reported in reciprocal centimeters. Only strong bands are reported unless otherwise stated. Proton NMR were obtained at 300 MHz with a Varian XL-300 instrument. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform, unless otherwise stated). Analyses were determined by our own analytical group. Methylene chloride was distilled from calcium hydride immediately prior to use. Chloroform was purified by filtration through a short column of neutral alumina (Woelm activity 1). All reactions were carried out under a nitrogen atmosphere in a flame-dried apparatus and were stirred magnetically unless otherwise specified. 3-(Methylsulfonyl)-1,2,4-triazine (1), and 5-phenyl-3-(methylsulfonyl)-1,2,4-triazine were prepared as described by Macor.[12]

4a,5,6,7,8,8a-Hexahydro-1-(methylsulfonyl)-8a-pyrrolidinylisoquinolin-6-one Ethylene Ketal (4). A solution of 1 (2.15 g, 13.5 mmol) and methylene chloride (15 mL) was chilled to 0 °C. A solution of 2 (2.84 g, 13.5 mmol) in methylene chloride (6 mL) was added dropwise over 10 min. During the addition, nitrogen evolution was vigorous. After the mixture was allowed to warm toward ambient temperature for 15 min, the solvent was removed in vacuo (at or below room temperature). The oily solid residue was triturated with ether–ethyl acetate and filtered to give 3.2 g (70%) of 4 as an analytically pure bright yellow solid: NMR δ 6.67 (dd, J = 1.5, 6.5 Hz, 1 H), 5.84 (dd, J = 5.0, 6.5 Hz, 1 H), 3.96–3.88 (m, 4 H), 3.08 (s, 3 H), 3.01–2.91 (m, 2 H), 2.81–2.69 (m, 2 H), 2.66–2.56 (m, 2 H), 2.11–1.80 (m, 3 H), 1.78–1.66 (m, 4 H), 1.62–1.54 (m, 1 H), 1.32–1.24 (m, 1 H); IR 2947, 2877, 1300, 1137, 1118 (sh), 1085 (sh), 1019, 953. Recrystallization from ethyl acetate caused much decomposition and a poor recovery of material with mp 131–134 °C. Anal. Calcd for $C_{16}H_{24}N_2O_4S$: C, 56.45; H, 7.11; N, 8.23. Found: C, 56.33; H, 7.07; N, 8.28.

Alternatively, the reaction could be worked up by cold concentration onto silica gel and flash chromatography with 25% ethyl acetate–hexanes. Cold concentration afforded the purified products as analytically pure yellow solids.

4a,5,6,7,8,8a-Hexahydro-1-(methylsulfonyl)-8a-pyrrolidinylisoquinoline (5) was prepared as above and obtained as a yellow solid in 65% yield after trituration with ether–hexanes: mp 57–58.5 °C; NMR δ 6.65 (dd, J = 1.5, 6.5 Hz, 1 H), 5.84 (dd, J = 4.5, 6.5 Hz, 1 H), 3.08 (s, 3 H), 3.01–2.92 (m, 2 H), 2.70–2.58 (m, 3 H), 2.46–2.38 (m, 1 H), 1.86–1.48 (m, 9 H), 1.32–1.20 (m, 1 H), 1.06–0.96 (m, 1 H); IR 2932, 2855, 1301, 1132, 952. Anal. Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85; N, 9.92. Found: C, 59.25; H, 7.66; N, 9.83.

4a,5,6,7,8,8a-Hexahydro-1-(methylsulfonyl)-3-phenyl-8a-pyrrolidinylisoquinoline (6) was prepared as above and obtained as a yellow solid in 78% yield after silica gel chromatography: mp 89–92 °C (hexane trituration); NMR δ 7.64 (dd, J = 1.5, 7.0 Hz, 2 H), 7.46–7.25 (m, 3 H), 6.27 (d, J = 4.5 Hz, 1 H), 3.23 (s, 3 H), 3.06–2.96 (m, 2 H), 2.79–2.68 (m, 1 H), 2.66–2.54 (m, 3 H), 1.92–1.54 (m, 9 H), 1.36–1.24 (m, 1 H), 1.14–1.02 (m, 1 H); IR 2932, 2865, 1302, 1133, 954. Anal. Calcd for $C_{20}H_{26}N_2O_2S$: C, 67.01; H, 7.31; N, 7.81. Found: C, 67.07; H, 7.24; N, 7.83.

1-(Methylsulfonyl)-5,6,7,8-tetrahydroisoquinolin-6-one Ethylene Ketal (3). A solution of 4 (0.341 g, 1.0 mmol) in methylene chloride (20 mL) was treated all at once with MCPBA (0.203 g, 1.0 mmol). The solution was stirred 3 h at ambient temperature; it was then diluted with methylene chloride and washed with 0.5 N sodium hydroxide, water, and brine. The organic phase was dried by filtration through Whatman 1PS filter paper and concentrated to give 0.265 g of 3, which was nearly pure by NMR. This product was redissolved in methylene chloride and filtered through a plug of silica gel with methylene chloride. Concentration gave 0.204 g (76%) of 3 as a white solid: mp 133–134 °C (ethyl acetate); NMR δ 8.23 (d, J = 5.0 Hz, 1 H), 7.13 (d, J = 5.0 Hz, 1 H), 4.01 (s, 4 H), 3.45 (t, J = 6.5 Hz, 2 H), 3.35 (s, 3 H), 3.02 (s, 2 H), 1.96 (t, J = 6.5 Hz, 2 H); IR 1295, 1120, 1105 (sh), 1060, 960. Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.44; H, 5.39; N, 5.11.

1-(Methylsulfonyl)-5,6,7,8-tetrahydroisoquinoline (7) was prepared as above as a white solid in 81% yield: mp 187–188 °C (ethyl acetate); NMR δ 8.18 (d, J = 5.0 Hz, 1 H), 7.13 (d, J = 5.0 Hz, 1 H), 3.34 (s, 3 H), 3.13 (t, J = 6.0 Hz, 2 H), 2.82 (t, J = 6.0 Hz, 2 H), 1.89–1.76 (m, 4 H); IR 3020, 2955, 1295, 1120, 960. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.70; H, 6.14; N, 6.63.

1-(Methylsulfonyl)-3-phenyl-5,6,7,8-tetrahydroisoquinoline (8) was prepared as above as a white solid in 70% yield: mp 128.5–130 °C (ethyl acetate–hexanes); NMR δ 7.91 (dd, J = 1.5, 6.5 Hz, 2 H), 7.59 (s, 1 H), 7.48–7.39 (m, 3 H), 3.46 (s, 3 H), 3.25 (t, J = 6.0 Hz, 2 H), 2.88 (t, J = 6.0 Hz, 2 H), 1.90–1.78 (m, 4 H); IR 3020, 2945, 1585, 1435, 1295, 1120, 955. Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.91; H, 5.91; N, 4.83.

One-Pot Synthesis of 7. A solution of 1 (0.165 g, 1.04 mmol) in methylene chloride (3 mL) was chilled to 0 °C. 1-Pyrrolidinylcyclohexene (0.167 mL, 1.04 mmol) in methylene chloride (1 mL) was added over 10 min. The solution was allowed to warm toward room temperature for 15 min. After chilling back to 0 °C, MCPBA (0.633 g, 3.12 mmol) was added in small portions over 1 min. The mixture was allowed to warm to ambient temperature and stir for 2 h. The solution was diluted with additional methylene chloride and washed successively with 0.5 N sodium hydroxide, water, and brine. Filtration drying through Whatman 1PS paper and concentration gave an off-white solid, which was flash chromatographed on silica gel with 15% ethyl acetate/hexanes to afford 0.083 g (38%) of 7 as a white solid, which had melting point and spectral data that were identical with that reported above.

Supplementary Material Available: Full details of the X-ray structural analysis of 4 (8 pages). Ordering information is given on any current masthead page.

(11) Gribble has recently demonstrated that the methylsulfonyl group is easily removed from the pyridine ring. See: Gribble, G. W.; Barden, T. C.; Johnson, D. A. *Tetrahedron* **1988**, *11*, 3195.

(12) Macor, J. E. Ph.D. Thesis, Princeton University, 1986.