Notes

Facile Synthesis of (+)-(*R*)-4-Methyl-2-cyclohexen-1-one

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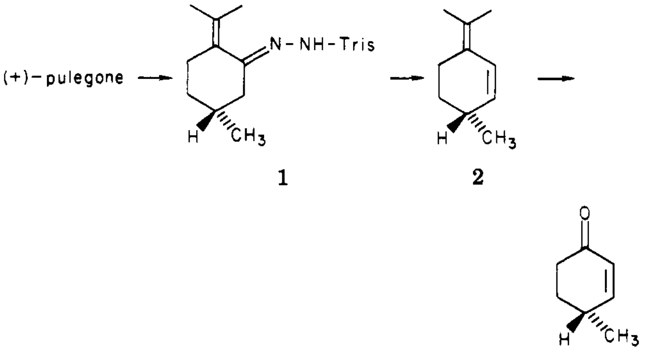
The use of chiral substances for the construction of optically active organic molecules has gained widespread popularity in recent years.[2] Our recent synthetic efforts required the ready availability of (+)-(*R*)-4-methyl-2-cyclohexen-1-one (**3**). Only one preparation of this enone has been reported,[3] starting from (*R*)-3-methylcyclohexanone. To avoid some of the problems inherent in this approach, we followed an alternative route and have found that the enone **3** can be conveniently prepared in modest yield by the selective ozonolysis of (+)-(*R*)-1-isopropylidene-4-methyl-2-cyclohexene (**2**).[4]

(+)-Pulegone reacts readily with 2,4,6-triisopropylbenzenesulfonohydrazide[5] and concentrated hydrochloric acid in methanol, to produce (+)-pulegone trisylhydrazone (**1**) in 80% yield. Compound **1** reacts rapidly with *n*-butyllithium in hexane/tetramethylethylenediamine (TMEDA) according to the procedure of Bond et al.[5] to produce the chiral diene **2** in 98% yield. The diene **2** is treated with ozone at −78 °C in methylene chloride[6] by using a sudan red 7B indicator.[7] With a dimethyl sulfide workup the chiral enone **3** is produced in 37% yield.



1 2 3

Although we are unable to claim 100% optical purity for this enone **3**, we have detected only single diastereomers when elaborating it with other chiral substrates.

Experimental Section

Technical (+)-pulegone and solvent red 19 (sudan red 7B) were purchased from Aldrich Chemical Co. and were used without further purification. TMEDA purchased from Aldrich Chemical Co., and hexane were dried and distilled from calcium hydride. 2,4,6-Triisopropylbenzenesulfonohydrazide was prepared according to the literature procedure from 2,4,6-triisopropylbenzenesulfonyl chloride.[8] Solvent red 19 was used as a 0.1% solution in methylene chloride. Ozonolyses were performed with a Welsbach T-23 ozonator. Silica gel used for flash chromatography[9] was Merck Type 60 (230–400 mesh). Infrared spectra were recorded on a Perkin-Elmer 283 B infrared spectrophotometer (neat for liquids and Nujol mulls for solids). NMR spectra were recorded in $CDCl_3$ solution (Me_4Si internal standard) on a Varian EM 360 A NMR spectrometer. Mass spectra were obtained on a Hitachi Perkin-Elmer RM-50 mass spectrometer (70 eV), and optical rotation determinations were made in chloroform at 22 °C on a Bellingham and Stanley, Ltd., optical polarimeter.

(+)-Pulegone 2,4,6-Triisopropylbenzenesulfonylhydrazone (1). To a stirred solution of 2,4,6-triisopropylbenzenesulfonohydrazide (25.2 g, 84.6 mmol) in 85 mL of reagent grade methanol at room temperature was added (+)-pulegone (12.9g, 84.6 mmol) followed by 1 mL of concentrated hydrochloric acid. The hydrazide immediately dissolved, and a precipitate began to form. The mixture was stirred for 10 min and placed in a freezer (−5 °C) for 12 h. The mixture was filtered, and the crystals were washed several times with cold methanol. The crystals were dried at high vacuum over P_2O_5 to yield 29.2 g (80%) of (+)-pulegone 2,4,6-triisopropylbenzenesulfonylhydrazone (**1**) as a white solid: mp 128 °C dec; $[\alpha]^{22}{}_D$ 27.6° *c* 16.7, $CHCl_3$); IR (Nujol) 3260, 1600, 1570, 1160, 690, 660 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 1 H), 7.15 (s, 2 H), 4.30 (septet, 2 H, $J = 7$ Hz), 2.90 (septet, 1 H, $J = 7$ Hz), 1.70 (m, 6 H), 1.25 (d, 18 H, $J = 7$ Hz), 0.95 (d, 3 H, $J = 6$ Hz); mass spectrum, m/e 432 (M^+).

(+)-(*R*)-1-Isopropylidene-4-methyl-2-cyclohexene (2). (+)-Pulegone 2,4,6-triisopropylbenzenesulfonylhydrazone (**1**; 9.4 g, 21.7 mmol) was dissolved in 200 mL of 80:20 hexane/TMEDA under N_2. The solution was cooled to −78 °C and treated with 3 equiv of 1.6 M *n*-butyllithium in hexane. After 20 min at −78 °C, the solution was warmed at 0 °C until the evolution of N_2 had ceased (~20 min). The reaction was quenched with water (35 mL), and the hexane layer was washed once with water and once with brine. The extract was dried ($MgSO_4$), filtered, and concentrated. The slightly yellow liquid was passed through a short column of silica with petroleum ether (bp 30–60 °C). Concentration gave 2.8 g (95%) of the desired olefin (**2**) as a colorless liquid: $[\alpha]^{22}{}_D$ 58.9° (*c* 17.7, $CHCl_3$); IR (neat) 3025, 1640, 1605 cm^{-1}; NMR ($CDCl_3$) δ 6.45 (dd, 1 H, $J_{1,2} = 10$ Hz, $J_{2,3} = 2$ Hz), 5.60 (dm, 1 H, $J = 10$ Hz), 1.80 (s, 6 H), 1.09 (d, 3 H, $J = 7$ Hz); mass spectrum, m/e 136 (M^+).

(+)-(*R*)-4-methyl-2-cyclohexen-1-one (3). Diene **2** (3.0 g, 22.0 mmol) was dissolved in 200 mL methylene chloride. To this solution was added 1 mL of a 0.10% sudan red 7B/methylene chloride solution. The red solution was cooled to −78 °C and ozonized until the red color began to lighten.[10] The solution was rapidly purged with N_2 for 10 min. The solution was treated with dimethyl sulfide (10 equiv) and allowed to warm to room temperature overnight. The CH_2Cl_2 solution was washed twice with water and once with brine. The extract was dried ($MgSO_4$), filtered, and concentrated. The crude **3** was purified directly by flash chromatography (100 g of silica, 15% ethyl acetate/85% low-boiling petroleum ether eluent) to give 0.90 g (37%) of the desired enone (**3**) as a colorless oil: bp 198 °C (760 mmHg); $[\alpha]^{22}{}_D$ 105° (*c* 9.2, $CHCl_3$); IR (neat) 3025, 1680, 1620 cm^{-1}; NMR ($CDCl_3$) δ 6.80 (d m, 1 H, $J = 10$ Hz), 5.95 (dd, 1 H, $J_{1,2} = 10$ Hz, $J_{2,3} =$

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[2] Szabo, W. A.; Lee, H. T. *Aldrichimica Acta* **1980**, *13*, 13 and references therein.

[3] Barieux, J. J.; Gore, J.; Subit, M. *Tetrahedron Lett.* **1975**, *22*, 1835.

[4] Dauben, W. G.; Lorber, M. E.; Vietmeyer, N. D.; Shapiro, R. H.; Duncan, J. H.; Tomer, K. *J. Am. Chem. Soc.* **1968**, *90*, 4762.

[5] Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

[6] The selectivity in this reaction is not observed in polar solvents such as methanol.

[7] Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

[8] Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1978**, *32*, 2157.

[9] Still, W. C.; Kahn, M.; Mitra, A.; *J. Org. Chem.* **1978**, *43*, 2923.

[10] We have found that neither the rate nor the scale of ozonolysis appreciably affect the yield of this reaction. Quenching the reaction early does not enhance the production of enone.

0022-3263/83/1948-2419$01.50/0

2 Hz), 1.18 (d, 3 H, J = 7 Hz); mass spectrum, m/e 110 (M^+).

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Registry No. 1, 85736-25-0; 2, 43124-56-7; 3, 75337-05-2; (+)-pulegone, 89-82-7.

Desiccant Efficiency in Solvent and Reagent Drying. 7. Alcohols[1-6]

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For many of their applications in synthesis, the lower monohydric alcohols are required to be scrupulously dry, and in contrast to alcohols containing six C atoms or more, whose desiccation does not appear difficult,[7] alcohols containing one to four C atoms have long been recognized as posing a formidable drying problem. In the case of ethanol for instance, numerous synthetic procedures contain statements such as "traces of water depress the yield considerably",[8] a practical result of which is that samples dried with CaO, for example (containing up to 5000 ppm of water), are often completely unacceptable.[9] There is also no doubt that for this group, as with other cases,[1-6] the problem of desiccant selection has been compounded by a lack of reliable quantitative data. As an illustration, when discussing the efficiency of magnesium or alkyl phthalate–Na as desiccants, many authorities[7c] continue to quote figures for water contents which were obtained in the original investigations[10] and which must now be viewed with some scepticism. In the light of this, we now report the results of a study of desiccant efficiency for this important group.

General Indications.[7c,11] Both chemical and absorptive-type desiccants have been proposed for drying alcohols, and these include[7c,11a,c] Al, BaO, CaO, Mg, Na, and K_2CO_3, while molecular sieves of Type 3A and 4A have been recommended for further drying.[11b] CaH_2 is also widely quoted,[11d] although some sources[11a] advise caution in its use with the lower alcohols.

While bearing in mind the well-known hygroscopic and hydrophilic properties of these compounds, the experiments reported below were not carried out by using any special techniques to obviate the entry of the atmosphere into drying systems other than those routinely used by the bench chemist.

Methanol. As one authority has observed,[11d] water is the dominant impurity in this solvent, and, unless *extraordinary* care is exercised, this content increases each time MeOH is handled. It is therfore quite remarkable that a survey of the literature on the drying of EtOH and MeOH points up a curious dichotomy: while references to EtOH[8,9] are characterized by numerous strictures as to the importance of achieving perfectly dry solvent, in contrast, MeOH is treated in a rather offhand manner, even though many of its applications parallel those of its higher homologue. "All MeOH used must be anhydrous" is a typical comment,[12] although information on how to realize this is lacking. The cause may lie in the belief that fractionation alone gives a solvent of adequate dryness, although the water content is still an admitted 1000 ppm.[7c,11d] Where drying methods have been indicated, the use of Mg seems most often advised.[11,13]

The results shown in Table I certainly suggest that, on the whole, MeOH is more difficult to dry than its higher homologue. These figures require little comment, but it is worth highlighting the poor performance of 3A molecular sieve powder for MeOH in comparison with other alcohols. This is almost certainly an effect of molecular size and nonselective adsorption on the large surface area which occurs *extremely rapidly* with this desiccant.[14] On account of its small size, MeOH is able to compete with water for entry into the sieve pore. Similar reasons also explain the relative ineffectiveness of the 4A and 5A bead forms of molecular sieve. On the other hand, the 3A *bead* form constitutes a useful desiccant, whose success is presumably due to a much slower rate of absorption which occurs with greater selectivity. It is also worth noting that a combination of methods is often the most effective strategy: a 1-L sample of MeOH distilled from Mg/I_2 onto 10% w/v 3A molecular sieve beads and then allowed to stand 48 h had residual water content of only 12 ppm. Finally, the unimpressive results obtained with BaO and CaO tend to support an earlier assessment of these agents as "tedious and wasteful".[15]

Ethanol. As stated above, references to the use of ethanol as a nucleophile,[16] as a solvent for Bouveault–Blanc

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[1] Part 1: Burfield, D. R.; Lee, K. H.; Smithers, R. H. *J. Org. Chem.* **1977**, *42*, 3060.

[2] Part 2: Burfield, D. R., Gan, G. H.; Smithers, R. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 23.

[3] Part 3: Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 3966.

[4] Part 4: Burfield, D. R.; Smithers, R. H. *J. Chem. Technol. Biotechnol.* **1980**, *30*, 491.

[5] Part 5: Burfield, D. R.; Smithers, R. H.; Tan, A. S. C. *J. Org. Chem.* **1981**, *46*, 629.

[6] Part 6: Burfield, D. R.; Smithers, R. H. *J. Chem. Educ.* **1982**, *59*, 703.

[7] The use of K_2CO_3 as a desiccant is often considered adequate in these cases. See for example: (a) Calzada, J. G.; Hooz, J. *Org. Synth.* **1974**, *54*, 63. (b) Paul, R.; Riobê, O; Maumy, M. *Ibid.* **1976**, *55*, 62. (c) Vogel, A. I. "Vogel's Textbook of Practical Organic Chemistry"; Longmans: London, 1978; p 270. See also, however: Crandall, J. K.; Rojas, A. C. *Org. Synth.* **1976**, *55*, 1.

[8] See: Weiner, N. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 279. Also relevant are the following quotations. (a) "Yields are poor if the alcohol is not completely dehydrated"; Lycan, W. H.; Puntambeker, S. V.; Marvel, C. S. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 319. (b) "Moisture in the reagents affects the yield seriously": Dox, A. W. "Organic Syntheses"; Wiley: New York, 1941; Collect, Vol. I, p 5. (c) "The use of 98% alcohol results in a lowering of yield by $^1/_3$": Kaufmann, W. E.; Dreger, E. E. *Ibid.*, p 258. (d) "The quality of absolute ethanol used has a very marked effect upon the yield": Adams, R.; Kamm, R. M. *Ibid.*, p 250.

[9] Thus, "Alcohol dried over lime gives very low yields": Ford, S. G.; Marvel, C. S. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 373. "Ethanol dried only by a lime process gives a low yield": Adkins, H.; Gillespie, R. H. *Ibid.*, 1955; Collect. Vol. III, p 672.

[10] For the use of magnesium see: Lund, H; Bjerrum, J. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 210. For the use of a sodium–alkyl ester combination see: (a) Smith, E. L. *J. Chem. Soc.* **1927**, 1288. (b) Manske, R. H. *J. Am. Chem. Soc.* **1931**, *53*, 1106.

[11] See: (a) Rickert, H.; Schwartz, H. In "Methoden der Organischen Chemie (Houben-Weyl)"; Mueller, E., Georg Thieme Verlag: Stuttgart, 1968; Band I/2, p 873. (b) Loewenthal, H. J. E. "Guide for the Perplexed Organic Experimentalist"; Heyden: London, 1980; p 50. (c) "Drying in the Laboratory"; E. Merck Co.: Darmstadt. (d) Riddick, J. A.; Bunger, W. B. "Organic Solvents", 3rd ed.; Wiley-Interscience: New York, 1970; pp 638–665.

[12] Helferich, B.; Schafer, W. "Organic Syntheses"; Wiley: New York, 1941; Collect. Vol. I, p 365.

[13] (a) Murray, J. I. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV. p 744. (b) Baumgarten, H. E.; Petersen, J. M. *Ibid.*, 1973; Collect. Vol. V, p 912.

[14] See ref 6.

[15] See Ref 11d, p 642.