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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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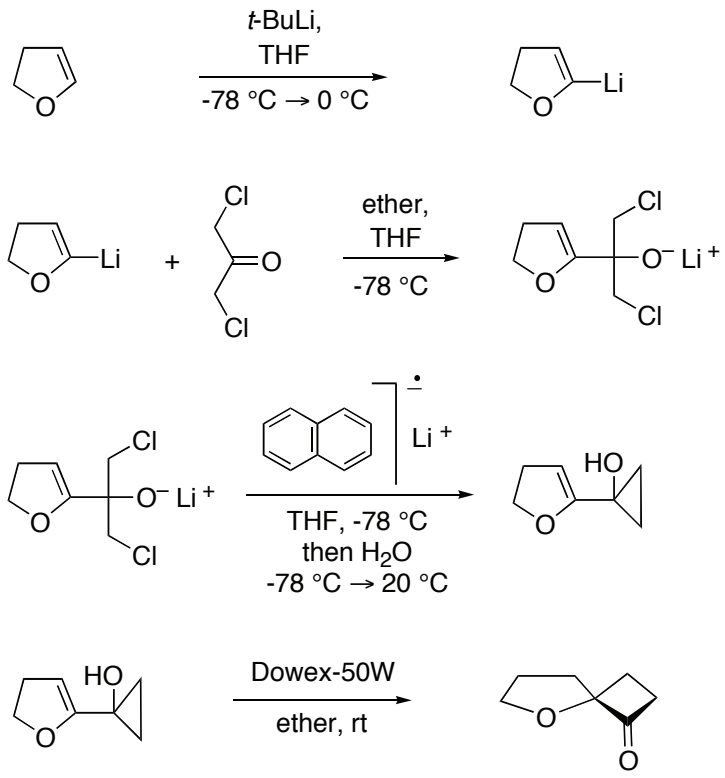
1,3-DICHLOROACETONE AS A CYCLOPROPANONE EQUIVALENT: 5-OXASPIRO[3.4]OCTAN-1-ONE



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1. Procedure

5-Oxaspiro[3.4]octan-1-one. Anhydrous tetrahydrofuran (100 mL) (Note 1) and 2,3-dihydrofuran (7.8 mL, 102 mmol, 1.3 equiv) (Note 2) are added to a single-necked 500-mL round-bottomed flask equipped with a rubber septum and previously purged with nitrogen. The magnetically stirred reaction mixture is cooled to –78 °C and 15 min later treated via cannula with *t*-butyllithium in pentane (1.7 M, 60 mL, 1.3 equiv) (Note 3) over 10 min. The resulting yellow solution is stirred in the cold for 30 min, at which point the acetone/dry ice bath is replaced by an ice-water bath and the reaction mixture is allowed to warm to 0 °C and kept at this temperature for 30 min (Note 4). Concurrently, dry ether (200 mL) and 1,3-

dichloroacetone (10.0 g, 78.8 mmol, 1.0 equiv) (Note 5) are placed in a rubber septum-fitted 1-L flask and cooled to –78 °C under nitrogen with stirring (Note 6). The lithiated dihydrofuran solution is next introduced via cannula over 20 min (Note 7). After 2 h at –78 °C, a solution of lithium naphthalenide in tetrahydrofuran (197 mL of 1 M, 2.5 equiv) (Note 8) is introduced via cannula during 20 min to give a dark green solution that is stirred at –78°C for 4–5 h and at room temperature overnight (Note 9). The reaction mixture is then cooled to 0 °C and quenched with saturated aqueous sodium bicarbonate solution (250 mL). The separated aqueous phase is extracted with ether (3 x 100 mL) and the combined organic layers are dried over $MgSO_4$ and filtered. The solution that contains the crude, unstable cyclopropanol is charged with 10 g of Dowex-50W (Note 10) and a stir bar. The solution is stirred overnight. Solvent evaporation is performed with care on a rotary evaporator at 20 °C and 50 mmHg until solvent evaporation ceased. The residue is chromatographed on ~450 grams of silica gel with 5-25% ether in hexanes as eluent (Note 11). The fractions containing the product are carefully concentrated through rotary evaporation as previously described. 5-Oxaspiro[3.4]octan-1-one is obtained (6.9 g, 70%) as a faint yellow oil (Note 12).

2. Notes

1. Anhydrous tetrahydrofuran (fresh Sure-Seal bottle) and ether (fresh 500 mL bottle) were obtained from Aldrich and J. T. Baker, respectively, and used as provided.

2. 2,3-Dihydrofuran (99%+ purity) was obtained from Aldrich and used as provided.

3. *t*-Butyllithium was obtained from Aldrich and used as provided. An atmosphere of nitrogen was maintained in all vessels throughout the reaction.

4. A color change from yellow to almost colorless was witnessed during the warming process.

5. 1,3-Dichloroacetone of 95% purity was obtained from Aldrich and recrystallized from 1:3 ether/hexane, mp 43 °C.

6. 1,3-Dichloroacetone is soluble in ether at room temperature, but crystallizes from this medium at –78 °C. Accordingly, the addition of the lithiated 2,3-dihydrofuran was to a white suspension in ether.

7. The white solid dissolved during the addition leaving a yellow solution. If the solution went turbid again before the addition of lithiated 2,3-dihydrofuran was completed, the product yield was significantly decreased. The use of a fresh bottle of *t*-butyllithium proved to be quite helpful in eliminating appearance of turbidity and ensuring good conversion to product.

8. Lithium naphthalenide was prepared as follows: To an oven-dried, 500-mL, one-necked, round-bottomed, septum-stoppered flask was added dry tetrahydrofuran (200 mL), naphthalene (25.3 g, 197 mmol), and a teflon-covered stir bar. The flask was purged with argon. To the resulting solution was added lithium wire (1.37 g, 197 mmol containing 0.6-0.8% sodium) in small chunks (3–5 mm long) that had previously been scraped under oil and rinsed in hexanes to remove the oxide coating. The mixture, which developed a deep-green color during 30 min, was allowed to stir overnight and was considered to constitute a 1 M solution.

9. The progress of the reaction was monitored by TLC on glass-backed plates. 1,3-Dichloroacetone was not visible by UV or *p*-anisaldehyde staining. However, the product, which had an R_f value of 0.38 in 3:1 hexanes/ether, stained faintly under these conditions.

10. The ion exchange resin of 100 or 400 mesh was washed in turn with 150 mL of 5% HCl, 100 mL of water, 300 mL of methanol, and 500 mL of ether, then dried overnight under high vacuum (0.1 mmHg) to give dried Dowex resin.

11. When solvent evaporation slowed, the solid that resulted was taken up in toluene (25 mL) and the residual liquid was loaded onto a column of silica gel. With 5% ether in petroleum ether as the eluent, naphthalene eluted in fractions 4-6 (each of 200 mL volume). The desired cyclobutanone eluted in fractions 9-19 following an increase in solvent polarity to 25% ether in hexanes. The purity of the product was quite acceptable at this stage. Attempts at distillation led to decomposition.

12. The analytical properties of the volatile title compound were as follows: R_f = 0.38 in 25% ether in hexanes; IR (neat, cm^{-1}) 2954 (s), 2876(s), 1788 (s), 1058 (s), 1021(s); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.87–1.95 (m, 3 H), 2.01–2.17 (m, 3 H), 2.60–2.77 (m, 2 H), 3.87 (t, J = 6.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 26.8, 33.9, 39.8, 70.2, 97.0, 211.9; MS (EI) *m/z* 127.06 $(M + H)^+$ calcd 144.05; Anal. Calcd. for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.24; H, 8.35.

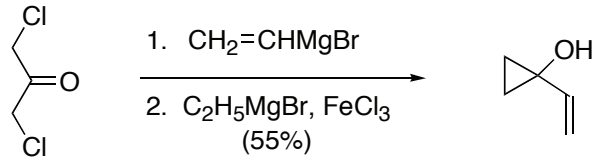
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

As a consequence of its highly reactive nature, cyclopropanone cannot conveniently be generated in preparative quantities in a laboratory setting.[2,3] Rather, the handling of this energetic compound has most often been made possible by virtue of its ability to undergo conversion to addition products from which the three-membered cyclic ketone may be released under relatively mild conditions. These precursors include the ethyl hemiketal,[4] 1-acetoxycyclopropanol,[5] and select carbinolamines.[6]

With the advent of 1,3-dichloroacetone as an article of commerce, an alternative cyclopropanone equivalent became available, although it has



been little recognized as such. Several decades ago, the capacity of the halogenated acyclic ketone to undergo 1,2-addition reactions with Grignard reagents such as vinylmagnesium bromide was recognized.[7] The subsequent introduction of C_2H_5MgBr and a catalytic quantity of $FeCl_3$ delivered 1-vinylcyclopropanol in 55% yield. Barluenga's subsequent contribution was to recognize that the reductive cyclization of the initial Grignard adducts could be carried out as well with anhydrous $MgBr_2$ and lithium powder, or more conveniently with lithium naphthalenide in THF.[8] The second and third steps of the present procedure constitute a modification of the latter protocol. The lithiation of 2,3-dihydrofuran is adapted from the literature,[9] while the final step has its foundation in the many oxonium ion-initiated pinacolic ring expansion reactions explored in this laboratory.[10]

The use of 1,3-dichloroacetone as a cyclpropanone equivalent leads exclusively to 1-substituted cyclopropanols. Consequently, competing processes open to the parent ketone such as decarbonylation,[11] ring opening,[12] polymerization,[5,13] and twofold addition to the carbonyl group[3] do

not operate. Advantageously, the present methodology is considered to be scalable, the only limitation being the need to remove naphthalene chromatographically. Finally, the chemistry here described is open to Grignard and organolithium reagents alike, and carries no restrictions as do cyclopropanone hemiacetals.[4]

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

2,3-Dihydrofuran; (1191-99-7)
1,3-Dichloroacetone: 2-Propanone, 1,3-dichloro-; (534-07-6)
Lithium naphthalenide: Naphthalene, radical ion(1-), lithium; (7308-67-0)
5-Oxaspiro[3.4]octan-1-one; (881389-73-7)

Leo Paquette was born in Worcester, Mass., obtained his B.S. degree in Chemistry from Holy Cross College in 1956, and was awarded the Ph.D. from M.I.T. in 1959 for his work on the synthesis of azasteroids with Norman Nelson. After 4 years as a medicinal chemist at the Upjohn Company, he joined the faculty at The Ohio State University where he quickly rose through the ranks to become Full Professor (1969-1981), Kimberly Professor (1981-1987), and University Distinguished Professor (1987-2003) prior to his retirement in 2004. Over the years, his research interests have spanned an enormous range from heterocyclic and hydrocarbon chemistry to the total synthesis of natural and unnatural products, the development of synthetic methodology and catalytic asymmetric methods, as well as chemistry based on organometallic and organosulfur reagents.

David Hilmey was born in Buffalo, NY in 1979. He received his B.S. in Medicinal Chemistry in 2001 from the State University of New York at Buffalo where he also conducted research on core-modified porphyrins under Professor Michael Detty. He then moved to The Ohio State University and obtained his Ph.D in 2006 under Professor Leo Paquette with research focused on heteroatom substituted spirocyclic scaffolds. He is currently a postdoctoral associate in the lab of Professor Tadhg Begley at Cornell University working on the chemical elucidation of thiamin biosynthesis.

Richard Todd Bibart was born in 1967 in Newark, Ohio. He received his B.A. in 1989 in chemistry from Wittenberg University, Springfield, Ohio, under the guidance of Nelson Sartoris. He received his Ph.D. from Stanford University in 1996 working with Dale Drueckhammer on the synthesis of Coenzyme A Analogs. After completion of his postdoctoral research with Leo Paquette in 1998, he joined the Regulatory and Analytical Sciences group at Merck and Co., Inc. He joined Pfizer in 2001 as a member of Analytical Research and Development.

Danny Lafrance was born in 1974 in Trois-Rivieres, Quebec, Canada. He received a B.Sc. degree in chemistry in 1996 from Laval University. He completed his M.Sc. at McGill University (Montreal, Canada) under the supervision of Professor Bruce A. Arndtsen, working on the insertion of imines and carbon monoxide into manganese-alkyl bonds. He then joined the process chemistry group of Schering-Plough, in New Jersey, where he worked for two years, before leaving for Montreal where he joined the Shire Biochem process chemistry group in 2001. He joined Pfizer in 2003 where he is working now in the Chemical Research and Development group.

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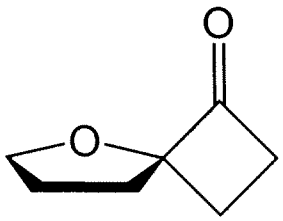

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