

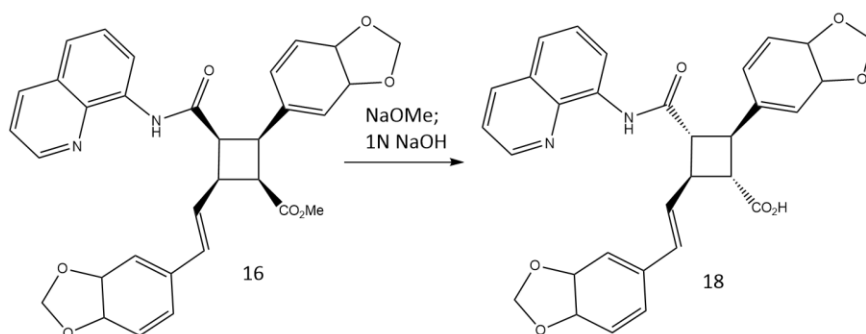
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CHEM 215.216 HH W14. STRUCTURED STUDY GROUP. NICHOLAS CARDUCCI.

GENERAL PROCEDURES

General procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), acetonitrile (CH₃CN), toluene (PhMe), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), methanol (MeOH) and triethylamine (Et₃N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO₄), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl₃ @ 7.26 ppm ¹H NMR, 77.16 ppm ¹³C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.¹

SYNTHESIS OF COMPOUND 18 FROM COMPOUND 16



A round bottom flask was flamed to sterilize and product 16 (386 mg, 0.70 mmol) was added and dissolved in THF (5.6 mL). A 1M solution of NaOMe in MeOH was prepared and then added the room temperature solution. The solution was then placed in a 45° C oil bath for 2 hours. For another hour, a 1M NaOH solution (1.4 mL, 1.4 mmol, 2 eq) was slowly added and stirred. During this reaction, the presence of starting material was monitored by TLC.

¹ Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, SI-2.

Afterwards, the reaction was cooled until it reached room temperature when diluted EtOAc (10 mL) was added; the reaction was quenched with 3M HCl (3M). The product was extracted in 10 mL of water and then ethyl acetate (4 x 5 mL). The organic layer was washed with brine (10 mL) and then dried over sodium sulfate. Finally, the product was concentrated *in vacuo*, producing product 18 in sufficient purity (light yellow foam, 368 mg, 98%)².

Physical state: white foam; R_f = 0.84 (silica gel, EtOAc); LCMS (m/z): calcd for C₃₁H₂₄N₂O₇, [M+H]⁺, 537.2; found, 537.2; IR (film) ν_{max}: br 2923, br 1680, 1527, 1488, 1250, 1038, 730 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 9.98 (s, 1 H), 8.80 (dd, J = 7.3, 1.8 Hz, 1 H), 8.60 (dd, J = 4.1, 1.8 Hz, 1 H), 8.17 (d, J = 8.2 Hz, 1 H), 7.59 – 7.48 (m, 2 H), 7.42 (dd, J = 8.3, 4.3 Hz, 1 H), 6.97 (dd, J = 4.2, 1.6 Hz, 2 H), 6.93 – 6.81 (m, 2 H), 6.76 (dd, J = 15.6, 8.0 Hz, 2 H), 6.63 (d, J = 15.8 Hz, 1 H), 6.27 (dd, J = 15.8, 7.3 Hz, 1 H), 5.93 (d, J = 5.4 Hz, 4 H), 4.03 (t, J = 9.7 Hz, 1 H), 3.59 (dd, J = 17.4, 8.5 Hz, 1 H), 3.18 (t, J = 9.6 Hz, 1 H), 3.15 (t, J = 9.7 Hz, 1 H).

¹³C NMR(1:1 MeOD:CDCl₃, 101 MHz): δ 174.5, 170.8, 147.7, 147.7, 147.5, 146.9, 146.3, 137.6, 136.4, 134.6, 133.3, 131.4, 130.8, 127.7, 126.9, 126.7, 121.9, 121.3, 120.8, 119.6, 116.8, 107.8, 107.7, 107.0, 105.2, 100.7, 100.6, 50.8, 47.5, 42.5, 42.2.

TECHNIQUES

OIL BATH

Oil baths are typically employed as heating elements when the temperature must be carefully controlled and when the reactants are flammable (and thus an open flame is not advised). In this case, an oil bath was likely employed since THF is flammable. The oil is heated on a hot plate and the temperature is monitored using a thermometer. Specialized equipment may include an immersion heating circulator, which evenly circulates heat throughout the vessel. Materials used in oil baths include medical paraffin, glycerol, silicon oil, cottonseed oil, or mineral oil. Disadvantages of using an oil bath include potentially spilling or spattering the oil and the extended amount of time needed to sufficiently heat the oil.

University of Wisconsin, Madison Department of Chemistry.
<http://www.chem.wisc.edu/areas/organic/orglab/tech/oilbath.htm> (accessed April 4, 2014).

Gelosa, D.; Sliepcevich, A. *Chemical Laboratory Techniques*; Milan, Italy, 2002; pp 4-5.

THIN LAYER CHROMATOGRAPHY

Thin layer chromatography is used primarily in the identification of compounds. Compounds move up the TLC plate based on polarity. Since the silica gel on the plate is highly polar, polar compounds adhere more strongly to the plate and move more slowly with the solvent up the plate (smaller retention factor, R_f). Conversely, nonpolar compounds have weaker interactions with the polar plate and stronger interactions with the comparatively more nonpolar solvent, moving farther up the plate (larger retention factor, R_f). Here, the reaction mixture was plated on 0.25 mm E. Merck silica gel plates (60F-254) and was visualized using an UV light. The solvent used was an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO₄), and heat.

² Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, SI-6-7.

Zubrick, J. W. *The Organic Chem Lab Survival Manual: A Student's Guide to Techniques*, 9th ed.; Massachusetts, 2014; pp 223-233.

EXTRACTION

Liquid/liquid extraction is a technique typically performed using a separatory funnel where two liquids are insoluble in one another, one in which the product is soluble and one in which any impurities are soluble. In this reaction, the layers were water and ethyl acetate (4 portions) and the layer containing the purified (extracted) product was collected. Additionally, after the organic layers were combined, they were washed with brine (saturated salt water). Brine is typically used to break up any emulsions and extract water. Finally, the solution was dried over sodium sulfate, a drying agent.

Zubrick, J. W. *The Organic Chem Lab Survival Manual: A Student's Guide to Techniques*, 9th ed.; Massachusetts, 2014; pp 128-135.

Massachusetts Institute of Technology Chemistry, http://ocw.mit.edu/courses/chemistry/5-301-chemistry-laboratory-techniques-january-iap-2012/labs/MIT5_301IAP12_Work_Handout.pdf (accessed April 4, 2014).

IN VACUO CONCENTRATION

Concentration *in vacuo* is used to remove liquid impurities. This technique is especially useful to evaporate volatile liquid impurities since, under a vacuum, vapor pressure doesn't prevent evaporation. In this reaction, concentration *in vacuo* was used to purify product 18.

University of Michigan Chemistry, <http://www.umich.edu/~chemh215/W06HTML/SSG2/ssg2/HTML%20Project/invacuo.htm> (accessed April 4, 2014).

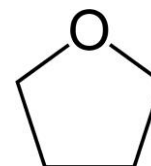
REAGENTS

TETRAHYDROFURAN (THF)

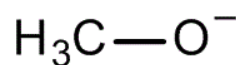
THF is a colorless liquid that is used as a monomer, chemical intermediate, and a commercial solvent. THF functioned as the solvent in this synthesis.

Corma, A.; Iborra, S.; Velty, A. *Chemical Reviews*, **2007**, *107*, 2411-2502.

MSDS: <http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=401757&brand=SIAL&PageToGoToURL=http%3A%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2F%2F401757%3Fflang%3Den>



SODIUM METHOXIDE (NAOME)



Sodium methoxide is a very basic solid that catalyzes many reactions (i.e. condensations, dehydrohalogenations) and acts as a nucleophile in $\text{S}_\text{N}2$ reactions. It is a flammable solid that can

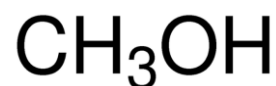
combust at 70-80° C. In this reaction, sodium methoxide deprotonated a hydrogen in the first step in the epimerization reaction.

Sodium Methoxide. *e-EROS Encyclopedia of Reagents for Organic Synthesis* [online]; Wiley & Sons, Posted September 15, 2006.

<http://onlinelibrary.wiley.com/doi/10.1002/047084289X.rs089m.pub2/abstract> (accessed Mar 28, 2014)

MSDS:<http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=164992&brand=SIAL&PageToGoToURL=ht tp%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2F%2F164992%3F%3F%3Den>

METHANOL (MEOH)



Methanol is used widely both in the lab and industrially. The largest use of methanol is in the production of methyl t-butyl ether (MTBE), which is a gasoline additive. Other uses of methanol are in dimethyl terephthalate, methylamines, chloromethanes, and methyl methacrylate. Additionally, methanol is often used as a solvent in car windshield wash, wall paints, and aerosol spray paint. In this reaction, methanol was used to protonate the carbanion in the second step of the epimerization reaction.

U.S. Environmental Protection Agency; Chemical Summary for Methanol. EPA 749-F-94-013a. 1994.

MSDS:<http://www.sigmaaldrich.com/MSDS/MSDS/PleaseWaitMSDSPage.do?language=&country=US&brand=SIAL&productNumber=322415&PageToGoToURL= http://www.sigmaaldrich.com/catalog/product/sial/322415?lang=en®ion=US>

SODIUM HYDROXIDE (NAOH)



Sodium hydroxide is a colorless noncombustible solid. Also known as lye, this extremely caustic reagent should be kept out of contact with water, as it can generate sufficient heat to ignite combustible materials. This reagent was used during the second reaction (acyl transfer)

Sodium Hydroxide. *NIOSH Pocket Guide to Chemical Hazards* [online]; Centers for Disease Control and Prevention, Posted November 18, 2010.

<http://www.cdc.gov/niosh/npg/npgd0565.html> (accessed Mar 31, 2014)

MSDS:<http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=164992&brand=SIAL&PageToGoToURL=ht tp%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2F%2F164992%3F%3F%3Den>

ETHANOL (ETOAC)



Ethanol is a clear, colorless liquid. Ethanol is easily absorbed by the human gastrointestinal tract and has antibacterial qualities. In the lab, ethanol is a common solvent and preservative. In this reaction, ethanol is the conjugate acid of the leaving group produced in the acyl transfer reaction.

Ethanol. *PubChem Compound* [online]; National Center for Biotechnology Information, posted no date cited.

<http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=702> (accessed Mar 31, 2014)

MSDS:<http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=E7023&brand=SIAL&PageToGoToURL=ht tp%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2F%2F7023%3F%3F%3Den>

HYDROCHLORIC ACID (HCL)

Hydrochloric acid is an extremely corrosive acid that is often used as a laboratory reagent. The most common way to synthesize hydrochloric acid is by dissolving hydrogen chloride in water. Additionally, hydrochloric acid is present in human gastric juices. In this reaction, HCl functioned in the acidic workup to make sure the product was protonated and not its conjugate base.



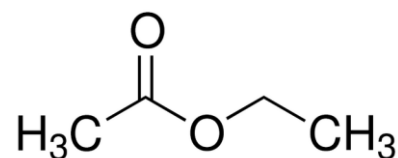
HCl. *PubChem Compound* [online]; National Center for Biotechnology Information, posted no date cited.

<http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=313> (accessed Mar 31, 2014)

MSDS: <http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=H1758&brand=SIGMA&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsigma%2Fh1758%3Fflang%3Den>

ETHYL ACETATE

Ethyl acetate is a common solvent used industrially for agrochemicals, inks, cosmetics, and adhesives. Although it is extremely flammable, it is not classified as dangerous for the environment. In this reaction, ethyl acetate was used in the extraction of product 18.



Rhodia: Member of the Solvay Group.

http://www.solvay.com/en/binaries/Ethyl_acetate_GPS_rev0_June12_RHD-139545.pdf (accessed April 1 2014)

MSDS: <http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=270989&brand=SIAL&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsigma%2F270989%3Fflang%3Den>

SODIUM SULFATE

Sodium sulfate is typically used as a drying agent in organic reactions. In nature, sodium sulfate occurs as mirabilite and thernadite deposits near salt lakes. Sodium sulfate is neutral and the anhydrous salt readily absorbs moisture. Industrially, sodium sulfate is used in laundry, dishwashing agents, and detergents.



Etacude: Sodium Sulfate, http://chemicals.etacude.com/s/sodium_sulfate.php (accessed April 1 2014)

MSDS: <http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=239313&brand=SIAL&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsigma%2F239313%3Fflang%3Den>