Organic Process Research & Development **1998**, *2*, 379−381

A Practical Synthesis of Cycloheptane-1,3-dione

John A. Ragan,* Teresa W. Makowski, David J. am Ende, Pamela J. Clifford, Gregory R. Young, Alyson K. Conrad, and Shane A. Eisenbeis

Process Research and Development, Pfizer Central Research, Eastern Point Road, Groton, Connecticut 06340

Abstract:

A three-step synthesis of cycloheptane-1,3-dione has been developed which avoids the use of heavy metal or explosive reagents and provides access to multigram quantities of this material.

We recently required a practical synthesis of cycloheptane-1,3-dione (**1**) for preparation of multikilogram quantities of a potential drug candidate. Several literature preparations of this compound were identified,[1−7] but none were deemed suitable for large scale preparation of clinical drug supplies (e.g., several used heavy metal or potentially explosive reagents, such as ethyl diazoacetate,[1] $PhHg(CBr_3)$,[3] $ClCH_2OCH_3$,[5] or $Hg(OAc)_2$[6]). Reported herein is a three-step synthesis of cycloheptane-1,3-dione from cyclopentanone, which proceeds in 58−64% overall yield and requires no purification of intermediates.

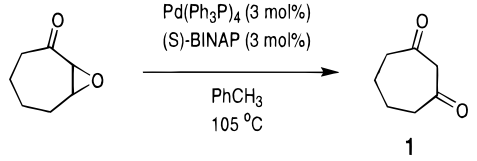
Discussion

Several synthetic approaches were considered prior to identification of the ultimately successful route. For example, Wacker oxidation of cyclohepten-3-one with *tert*-butylhydroperoxide and $PdCl_2$ was found to be selective for the desired 1,3-diketone, as anticipated on the basis of a literature report.[8] However, a *tert*-butyl impurity contaminated the product diketone and adversely affected the subsequent steps in the sequence.

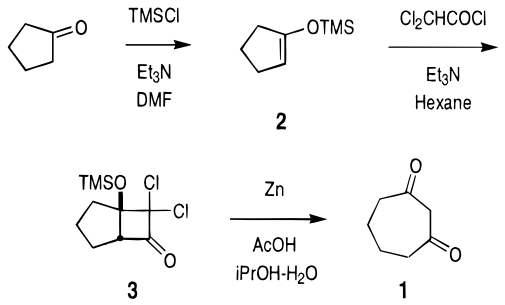
Another route investigated was Noyori's palladium-mediated rearrangement of 2,3-epoxycycloheptanone to cycloheptane-1,3-dione (Scheme 1).[4] As per the original report, using 4−8 mol % of $Pd(Ph_3P)_4$ and 1,2-bis(diphenylphosphino)ethane (dpe), complete conversion to the desired diketone was realized in 12−16 h. We also found that using BINAP in place of dpe allowed the catalyst load to be reduced to 2−3 mol % without adversely affecting the rate of rearrangement.[9] Ultimately, however, the cost of reagents and access to the epoxide[10] were deemed prohibitive for a multikilogram campaign.

A shorter, more practical synthesis of cycloheptane-1,3-dione was realized upon consideration of a two carbon ring

Scheme 1



Scheme 2



expansion from cyclopentanone (Scheme 2). Our plan was to utilize the known[11] [2 + 2] adduct **3** of dichloroketene and 1-(trimethylsiloxy)cyclopentene, which contains the requisite seven carbon atoms and has the proper 1,3-oxygen substitution for cycloheptane-1,3-dione. This strategy has direct precedent in the work of Pak et al.,[12] who reported a two-step conversion of 3-trimethylsiloxy-2,2-dichlorocyclobutanones into 1,3-diketones via Bu_3SnH-mediated dechlorination to the 3-trimethylsiloxycyclobutanone, followed by Bu_4NF-induced desilylation and ring opening to the 1,3-diketone.[13−15] While this work provides excellent precedent for the strategy, Bu_3SnH was clearly unacceptable for our purposes due to both handling toxicity and potential contamination of clinical drug supplies.

Zinc−acetic acid is a well precedented reagent for reduction of 2,2-dichloroketones.[16] While numerous examples of 2,2-dichlorocyclobutanone reductions are found

* To whom correspondence should be sent. Phone (860) 441-6334.

(1) Eistert, B.; Haupter, F.; Schank, K. *Liebigs Ann. Chem.* **1963**, *665*, 55−67.
(2) Maclean, I.; Sneeden, R. P. A. *Tetrahedron* **1965**, *21*, 31−34.
(3) Hutmacher, H.-M.; Kruger, H.; Musso, H. *Chem. Ber.* **1977**, *110*, 3118−3125.
(4) Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 2095−2096.
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(6) Bhusan, V.; Chandrasekaran, S. *Synth. Commun.* **1984**, *14*, 339−345.
(7) Vankar, Y. D.; Chaudhuri, N. C.; Rao, C. T. *Tetrahedron Lett.* **1987**, *28*, 551−554.
(8) Tsuji, J.; Nagashima, H.; Hori, K. *Chem. Lett.* **1980**, 257−260.
(9) Most experiments were performed with (*S*)-BINAP, and (*R*)-BINAP was equally effective. To our surprise, racemic BINAP led to incomplete conversion (<20%). Remarkably, using the same bottles of (*S*)- and (*R*)-BINAP which worked well at 3 mol %, an "artificial" racemate from 1.5 mol % each of the (*S*)- and (*R*)-enantiomers also failed. These results have yet to be adequately explained (and are particularly perplexing since the substrate is racemic and the product diketone is achiral).
(10) The epoxide was prepared in three steps from cycloheptanone: (i) Br_2, THF−H_2O; (ii) Li_2CO_3, LiBr, DMF; (iii) H_2O_2, NaOH, MeOH.
(11) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 3173−3179.
(12) Pak, C. S.; Kim, S. K.; Lee, H. K. *Tetrahedron Lett.* **1991**, *32*, 6011−6014.
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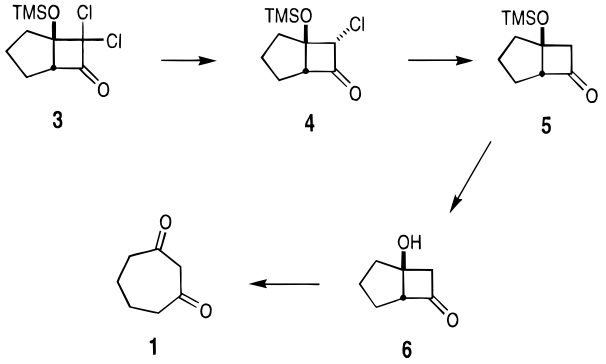
(14) Brady, W. T.; Lloyd, R. M. *J. Org. Chem.* **1979**, *44*, 2560−2564.
(15) Footnote 11 in ref 13 states that dechlorination of **3** (Bu_3SnH) followed by desilylation with Bu_4NF does, indeed, form cycloheptane-1,3-dione. No experimental details are provided.
(16) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163−344.

10.1021/op9802069 CCC: $15.00
Published on Web 10/07/1998

Scheme 3



in the literature,[17−19] to our knowledge there are no such examples with 3-trimethylsiloxy-2,2-dichlorocyclobutanones. (There is one example of a 3-alkoxy-2,2-dichlorocyclobutanone reduction with Zn/AcOH.[20] In addition, Grieco et al. have reported the Zn/AcOH reduction of a 2,2-dichlorocyclobutanone containing a *tert*-butyldimethylsilyl ether several atoms removed;[21] the TBS ether is stable to the reaction conditions.) Thus, we were gratified to find that direct treatment of dichlorocyclobutanone **3** with zinc (powdered or −30+100 mesh granules) and acetic acid in aqueous 2-propanol cleanly provided the desired diketone **1**.

The overall yield of crude diketone from cyclopentanone is 58−64%. This material is a dark orange oil, which is ca. 80−90% pure by ^{1}H NMR and is suitable for subsequent reactions. If desired, the crude product can be purified by distillation, which provides a colorless liquid in 38% overall yield from cyclopentanone. In our application, we found that the subsequent reactions were equally efficient with crude or distilled diketone; thus, overall yields were substantially higher when the distillation was omitted.

GC/MS monitoring of the reaction showed several intermediate products (Scheme 3). The monochloroketone **4** began to form immediately upon addition of AcOH (and in some cases was observed with just zinc treatment, prior to addition of any acid). Shortly thereafter (30−60 min), the fully reduced cyclobutanone **5** began to form. After 2−6 h of reaction, an intermediate GC/MS peak was observed which was isomeric with the desired diketone. This peak was tentatively assigned as bicyclic keto-alcohol **6**. After 6−18 h, all intermediates had been converted to the desired diketone (**1**).

In one experiment, the reaction was monitored with an in situ IR probe. As the AcOH was added to the reaction, the C═O absorption of the AcOH began to obscure this region of the spectrum. Early in the run, however, an intermediate C═O absorption was observed at 1787 cm^{-1}. Under the reaction conditions, dichloroketone **3** had a C═O stretch at 1803 cm^{-1} (lit.[11] 1805 cm^{-1}), and a neat sample of diketone **1** absorbed at 1718 and 1698 cm^{-1} (lit.[3] 1716 and 1693 cm^{-1}). We have tentatively assigned the 1787 cm^{-1} intermediate as monochloroketone **4**; this is most consistent with the GC/MS data (intermediate **5** was not observed until later in the reaction, by which time the AcOH had obscured the C═O region) and is consistent with the literature report for a neat sample of ketone **4** (1795 cm^{-1})[22] (ketone **5** is reported to absorb at 1777 cm^{-1}).[13]

On laboratory scale runs of the Zn/AcOH reduction (5−150 g), moderate exotherms were observed. Concern over the heat flow associated with larger scale reductions (>50 kg) led us to examine the reaction in a Mettler RC1 reaction calorimeter. This was run on 50 g of dichlorocyclobutanone **3** in 270 mL of 1:1 2-propanol−water, with dropwise addition of 100 mL of 50% aqueous acetic acid over a period of 4 h. These studies showed an exotherm of 500 kJ/mol (120 kcal/mol), which translated to a maximum adiabatic temperature rise of 65−70 °C (this represents a "worst case scenario", i.e., if the AcOH were added rapidly, with no external cooling, the maximum temperature reached from an initial temperature of 25 °C would be ca. 90−95 °C). From an operational safety point of view, these data were viewed as acceptable. (The Zn reduction has been run on 100 kg scale in the pilot plant without incident.)

Conclusion

In summary, we have identified a three-step synthesis of cycloheptane-1,3-dione, which proceeds in 58−64% overall yield, requires no purification of intermediates other than standard aqueous workups, and avoids the use of costly or toxic reagents. A laboratory scale (50 g) procedure is provided herein, and the sequence has been used to provide multikilogram quantities of cycloheptane-1,3-dione in the pilot plant.

Experimental Section

All chemicals were used as purchased. Dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased in anhydrous form from Aldrich in Sure-Seal glass bottles; all other solvents were reagent grade. Reactions were run under a positive pressure of nitrogen unless otherwise stated. 400 MHz ^{1}H (and 100 MHz ^{13}C) NMR spectra were obtained on a Varian Unity+400 spectrometer equipped with two rf channels, indirect detection, and pulsed-field gradients (*z*-axis only). ^{1}H spectra were acquired using 45° acquisition pulses, 3.0 s recycle delay, and 16 scans at a resolution of 0.2 Hz/point. The acquisition window was typically 6800 Hz, and processing used 0.1 Hz line broadening. ^{13}C spectra were acquired using 45° acquisition pulses, 0.7 s recycle delay, and 512 scans at a resolution of 0.8 Hz/point. Proton decoupling was applied at 3 W of power during acquisition, and 2 Hz line broadening was used during processing. Mass spectral data were collected on either a Hewlett-Packard GC/MS (electron impact ionization) or a Micromass (Fisons) Platform II mass spectrometer (atmospheric pressure chemical ionization). Thin-layer chromatography (TLC) was

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performed on precoated sheets of 60 F254 (Merck Art. 5719). Melting points are uncorrected.

1-(Trimethylsiloxy)cyclopentene (2). The procedure is a slight modification of that reported previously.[23] A 1 L round-bottom flask is charged with cyclopentanone (50.7 g, 0.603 mol) and DMF (250 mL). Triethylamine is added (200 mL, 1.45 mol), followed by dropwise addition of TMSCl (91 mL, 0.72 mol) over 5 min. The solution is then warmed to reflux (90 °C) for 26 h. After cooling to ambient temperature, the mixture is transferred to a separatory funnel, rinsing with 500 mL of hexanes. The solution is washed with water (three portions of 100 mL each) and brine (100 mL) and then concentrated to give 110 g of a dark orange oil. ^{1}H NMR analysis showed the desired product plus 10−15% of triethylamine. This material was used in the next reaction without further purification.

7,7-Dichloro-1-(trimethylsiloxy)bicyclo[3.2.0]heptan-6-one (3). The procedure is a slight modification of that reported previously.[11] The crude TMS enol ether (**2**) (0.60 mol) is dissolved in 950 mL of hexanes in a 2 L round-bottom flask. Triethylamine (100 mL, 0.72 mol) is added, followed by dichloroacetyl chloride (58 mL, 0.60 mol) as a solution in 450 mL of hexanes, dropwise over 2 h. The solution is then stirred at ambient temperature overnight. The reaction mixture is then filtered through fritted glass, rinsing with several 50 mL portions of hexane. The clear solution is concentrated in vacuo to provide 128 g (80% over two steps) of product as a dark brown oil. This material is homogeneous by GC/MS and ^{1}H NMR (spectra as reported in ref 11), save traces of Et_3N and DMF, and is used directly in the next reaction.

Cycloheptane-1,3-dione (1). Dichlorocyclobutanone **3** (128 g, 0.48 mol) is dissolved in 520 mL of 1:1 2-propanol−water in a 2 L, three-neck flask with an overhead stirrer. Zinc granules (126 g, 1.9 mol, −30+100 mesh) are added in one portion. After 60 min at room temperature, a mixture of 130 mL of AcOH plus 260 mL of water is added dropwise via addition funnel (ca. 4 mL added initially, followed by a 10 min hold to check for exotherms; 20 mL then added, followed by another 10 min hold; the remaining acid solution is then added dropwise; the entire addition takes 1.5−2 h). After 16 h, the mixture is transferred to a separatory funnel, decanting away from most of the zinc (several small 2-propanol rinses are used). The 2-propanol−AcOH−water mixture is then extracted with five portions of toluene (250 mL each), which are combined and concentrated to provide 51.7 g of product as a dark, orange-brown oil (85% crude mass balance, ca. 85% pure by ^{1}H NMR). This material is suitable for subsequent reactions or can be purified by distillation, which provided 29.4 g (0.23 mol, 48% yield) of product as a clear, colorless oil (bp 65−75 °C at 1.2 mm). The spectral properties (^{1}H NMR, GC/MS) were identical to those of samples prepared by the oxymercuration route of Bhusan and Chandrasekaran.[6]

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Acknowledgment

The authors thank Alex Grodski and Gary Berg for samples of cycloheptane-1,3-dione prepared by another route,[6] and Drs. Stephane Caron, Frank Urban, Tamim Braish, and Keith McCarthy for numerous helpful discussions.

Received for review December 17, 1997. Accepted August 19, 1998.

OP9802069