Tetrahedron Letters 52 (2011) 1871–1873

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A mild, large-scale synthesis of 1,3-cyclooctanedione: expanding access to difluorinated cyclooctyne for copper-free click chemistry

Evan A. Sims [a], Cole A. DeForest [a], Kristi S. Anseth [a,b,*]

[a] Department of Chemical & Biological Engineering, University of Colorado, Boulder, CO 80309, USA
[b] Howard Hughes Medical Institute, University of Colorado, Boulder, CO 80309, USA

ARTICLE INFO

Article history:
Received 15 January 2011
Revised 2 February 2011
Accepted 4 February 2011
Available online 4 March 2011

Keywords:
Copper-free click chemistry
Wacker–Tsuji oxidation
Cyclooctanedione
Difluorinated cyclooctyne

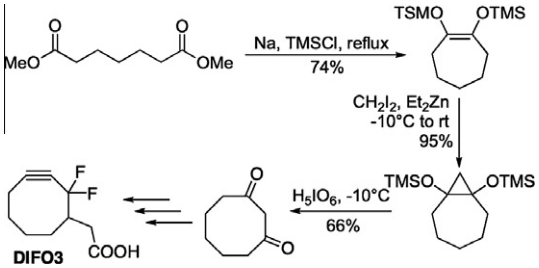
ABSTRACT

We report the large-scale synthesis of 1,3-cyclooctanedione in five steps with 29% yield. This molecule is a synthetic precursor to difluorinated cyclooctyne, which participates in a bioorthogonal copper-free click reaction with azides. The final step demonstrates the first successful application of the Wacker–Tsuji oxidation to form a cyclic 1,3-dione.

In the past decade, bioorthogonal conjugation methods have emerged as powerful and increasingly indispensable tools for performing chemistry in biological contexts.[1–3] Notably, the strain-promoted azide–alkyne cycloaddition (SPAAC) has proven especially promising as a cytocompatible ligation method. The reaction boasts nearly all the advantages of the canonical copper(I)-catalyzed Huisgen [2+3] cycloaddition between an azide and a terminal alkyne, but requires no copper catalyst, which is cytotoxic at >0.1 mM concentrations.[4,5] Thus, the chemistry can be performed readily ($k \sim 10^{-1}$ M^{-1} s^{-1}) in the presence of individual cells as well as full living organisms.[6] Bertozzi and co-workers have pioneered the synthesis of several cyclooctyne reagents and have successfully applied their use as chemical probes to perform in vivo imaging to study glycosylation in zebrafish and mice.[7,8] In addition, other molecules for strain-promoted reactions with azides have recently been developed including (aza-)dibenzocyclooctynes,[9,10] biarylazacyclooctynone,[11] and oxanorbornadienes[12] which exhibit similar utility.

More recently, the use of Cu-free click chemistry has expanded from simple labeling procedures to include the formation of complex materials.[13–15] By end-functionalizing synthetic polypeptides with a difluorinated cyclooctyne reagent (DIFO3)[16] and reacting with a four-arm poly(ethylene glycol) tetraazide in an aqueous medium, hydrogels are formed that allow for the direct encapsulation of cells.[13,15] Despite this preliminary success, the difficulty of the cyclooctyne synthetic preparation has ultimately hampered the widespread implementation of SPAAC in material formation to date. Additionally, utilizing these reagents in material fabrication requires gram-quantities of the reagents as opposed to the μg- to mg-scale required for labeling experiments. Thus, we sought to develop an improved synthetic route that enables DIFO3 to be formed on the multi-gram scale.

We found the main difficulty in preparing DIFO3 in a significant quantity lies in producing large amounts of the key synthetic intermediate 1,3-cyclooctanedione. The published route of Pirrung and Webster[17] (Scheme 1) for the preparation of this compound has several undesirable characteristics, including the use of large molar equivalents of water-reactive sodium metal and diethylzinc.[18] Pyrophoric organometallic reagents are not ideal for larger scale reactions and have in some cases been implicated in laboratory accidents.[19] Moreover, the acyloin condensation (Scheme 1, first step) exhibited highly-variable yields in our hands. This is in part



Scheme 1. Traditional synthesis of DIFO3 from 1,3-cyclooctanedione intermediate.

* Corresponding author. Tel.: +1 303 492 7471; fax: +1 303 492 4341.
E-mail address: Kristi.Anseth@colorado.edu (K.S. Anseth).

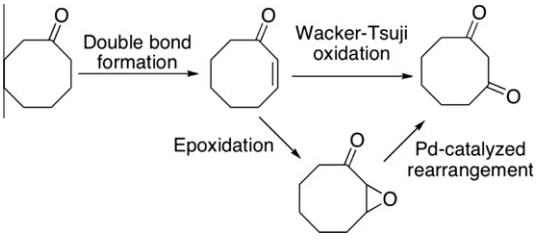
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.02.029

due to the nature of cyclizing larger rings: significant oligomerization/polymerization likely occured, as evidenced by the formation of a non-volatile, colored byproduct and reduced product recovery, even with high dilution and slow addition of diester. Thus, we sought to develop a mild, high-yielding synthesis of 1,3-cyclooctanedione starting from an inexpensive, readily-available substrate.

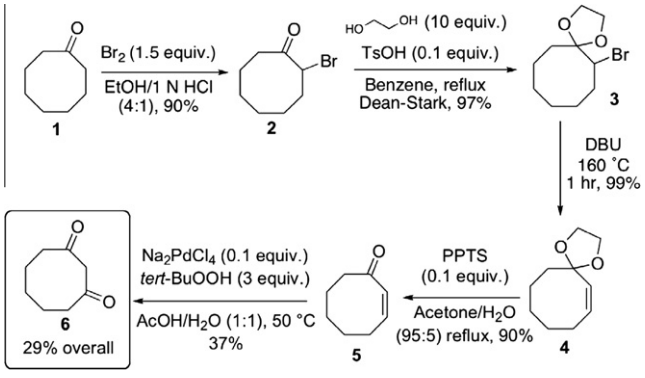
Initially, we were inspired by a kg-scale preparation of 1,3-cycloheptanedione,[20,21] whose key step relies on the cycloaddition between dichloroacetyl chloride and 1-trimethylsilyloxycyclopentene. We hypothesized that this synthetic approach could be easily adapted to prepare 1,3-cyclooctanedione. However, we abandoned this route after experiencing difficulty obtaining significant coupling between 1-trimethylsilyloxycyclohexene and dichloroacetyl chloride. Ultimately, cyclooctanone was chosen as a starting point as it is inexpensive ($77 per 100 g via Aldrich), readily available, and several potential methods for installing the ketone functionality at the β-position were identified, including epoxidation and subsequent Pd-catalyzed rearrangement[22,23] as well as the direct Wacker–Tsuji oxidation[24] (Scheme 2).

From the starting cyclooctanone (**1**), enone **5** was synthesized in four steps and 78% yield via α-bromination followed by elimination, an established method to introduce an α,β C=C double bond.[25] Bromination of ketone (**1**) was accomplished in excellent yield (90%, Scheme 3) with 1.5 equiv of Br_2 in ethanolic hydrochloric acid and the product was pure enough after standard aqueous workup to obviate chromatographic purification.

Many attempts to effect direct dehydrobromination on **2** with various bases and solvent systems were made (KOH in isopropanol, DBU in toluene or dichloromethane,[26] and LiBr/Li_2CO_3 in DMF[27]). All such attempts, however, failed to generate significant quantity of enone **5**. Thus, a two-step protection/deprotection of the ketone moiety was adopted.[28] Formation of bromo ketal **3** under Dean–Stark conditions was achieved in near-quantitative yield and reasonable purity. Quantitative dehydrobromination of crude ketal bromide **3** was accomplished after reacting for 1 h in neat 1,8-diazabicycloundec-7-ene (DBU) at 160 °C. We note that the direct conversion of cyclooctanone **1** to the bromo ketal **3** has been reported elsewhere.[29,30] Crude product **4** was deprotected via *trans*-ketalization in PPTS/acetone/water, and resultant enone **5** was recovered in high yield after purification by flash chromatography. Note that while Plumet[23] reports a method to synthesize enone **5** in two steps from cyclooctanedione, we feel the extra two steps for the present scheme are justified: The overall yield is higher (78% vs 49%), both require just one chromatographic purification (for the final enone), and the palladium reagent used in the Plumet method (73 mol %) would add considerable cost to a large scale preparation.



Scheme 2. Strategy for synthesis of 1,3-cyclooctanedione.



Scheme 3. Complete synthesis of 1,3-cyclooctanedione (**6**) from cyclooctanone (**1**) with reaction conditions and obtained yields. Full reaction conditions, as well as ^1H, ^{13}C, and COSY NMR and HR-MAS characterization for all compounds can be found in the Supplementary data.

Table 1
Isolated yields of dione (**6**) via the Wacker–Tsuji oxidation of enone (**5**) for a variety of catalyst and reactant amounts, as well as temperature

Na_2PdCl_4 (mol equiv)	*tert*-BuOOH (mol equiv)	Temperature (°C)	Yield (%)
0.2	1.5	50	24
0.2	1.5	100	11
0.2	3	50	36
0.2	3	30	36
0.1	1.5	50	30
0.1	3	50	37
0.4	1.5	50	22

Two potential methods to convert enone **5** to 1,3-cyclooctanedione (**6**) were identified involving epoxidation then palladium-catalyzed rearrangement.[31,23] However, after an initial attempt to form the epoxide from enone (**5**) under Weitz–Scheffer conditions (aq H_2O_2 or TBHP and cat. NaOH)[32] failed, we found that Wacker–Tsuji oxidation conditions gave the desired dione in a single step (Scheme 3).[24] After briefly screening reaction conditions (Table 1), conversion of enone **5** to dione **6** was realized in 37% yield by treatment with 0.1 equiv Na_2PdCl_4 and 3 equiv *tert*-BuOOH in AcOH/H_2O (1:1) at 50 °C—undesired formation of unidentified side products resulted in the modest yield of this step. Given the high yields and simple purifications for the preceding steps, even with a yield <40% for the final step, this represents a significant improvement over the standard method for 1,3-cyclooctanedione preparation (Scheme 1).[17] Furthermore, to the best of our knowledge, no successful application of the Wacker–Tsuji application to a cyclic substrate has ever been reported.

In summary, we have described a new method to synthesize 1,3-cyclooctanedione in five steps (Scheme 3) using an inexpensive starting material, robust reactions, and with only two steps requiring chromatographic purification. In addition, the first successful application of the Wacker oxidation in the direct synthesis of a cyclic 1,3-dione is shown. Using this method, we were able to generate 15+ g of dione **6** in 29% overall yield which can be used to further synthesize DIFO3 for SPAAC.

Acknowledgments

The authors would like to thank C. Bertozzi and J. Baskin for initial communication concerning these efforts. This work was funded by the Howard Hughes Medical Institute. Fellowship assistance to C.A.D. was awarded by the US Department of Education's Graduate Assistantships in Areas of National Need program.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.029.

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