Tetrahedron Letters 56 (2015) 386–389

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Improved synthesis of and nucleophilic addition to 2-formyl-2-cyclohexenone

Elan M. Adary [†], Chih-wei Chang [†], Damian T. D' Auria [†], Phuc M. Nguyen [†], Klaudyna Polewacz [†], Justin A. Reinicke, Hannah Seo [†], Gideon O. Berger [*]

Department of Natural Sciences, Hawai'i Pacific University, Honolulu, HI 96813, United States

ARTICLE INFO

Article history:
Received 22 October 2014
Revised 17 November 2014
Accepted 22 November 2014
Available online 3 December 2014

Keywords:
2-Formyl-2-cyclohexenone
2-Formyl-2-cycloalkenone
Michael addition
Dimethylmalonate
Conjugate addition

ABSTRACT

A preparation of 2-formyl-2-cyclohexenone in nearly quantitative yield and purity of approximately 95% is described. It is scalable and has been extended to the synthesis of the 5- and 7-membered ring homologs with comparable yields. Conditions have also been developed for the successful conjugate addition of dimethylmalonate to 2-formyl-2-cyclohexenone, in good and scalable yield (60%). This result has been extended to 5 other nucleophile classes, and the dimethylmalonate conjugate addition has been demonstrated with 2-formyl-2-cyclopentenone and 2-formyl-2-cycloheptenone.

Introduction

2-Formyl-2-cyclohexenone (**1**) has enjoyed a variety of important applications in synthesis (Fig. 1). In particular, it has been utilized in a range of cycloaddition reactions. Interestingly, **1** has played both roles in 4+2 cycloadditions, as a doubly-activated dienophile[1] and as a heterodiene.[2] In earlier work, Meyer and coworkers attempted to conduct a Michael addition to **1**, by reacting it with a β-ketoester enolate in an effort to achieve a subsequent annulation reaction.[3] However, Meyer reported that traditional Michael reactions were unsuccessful with **1** due to enolization at the γ-carbon, providing the Michael-unreactive **2**. Indeed, they found this side reactivity to be a problem with any 2-formyl-2-cyclohexenone derivative that was not doubly substituted in the γ-position (see **3** and **4**). To get around this problem Meyer was able to conduct a successful conjugate addition with an enamine alternative and ultimately effect the same type of annulation.[4] Nonetheless, we wished to revisit this chemistry in hopes that a successful Michael addition conducted upon **1** could serve as a general entry into the iridoids and related compounds.

The literature preparations of 2-formyl-2-cyclohexenone, which all utilize 2-oxocyclohexanecarbaldehyde, are problematic for a variety of reasons including low yield, toxicity of reagents, difficulty in purification, degradation, and lack of scalability.[3,5–7] Much of the difficulty in developing a robust preparation may stem from the inherent instability of **1** and the related difficulty of its purification. Because we wished to use **1** as the starting material for total synthesis projects, our first order of business was to develop an improved preparation.

Results and discussion

Given the availability of inexpensive, non-toxic, and high yielding alcohol oxidation reagents we decided to approach this problem by oxidizing 2-(hydroxymethyl)-2-cyclohexenone (**5**), readily available in high yield and large scale from the Baylis–Hillman reaction of cyclohexenone and formaldehyde with 4-dimethylaminopyridine.[8] Our oxidant of choice was Dess–Martin periodinane (DMP) and in our initial attempts involving a traditional aqueous work-up we found that the crude material was of poor and varying purity. Furthermore, we found that chromatography only reduced the purity of the product. Suspecting that aqueous work-up was accelerating the degradation we decided to try a different approach by first exchanging the reaction solvent for a smaller volume of 30% ethyl acetate/hexane mixture and then quickly filtering the crude solution through a short silica gel *plug* in order to capture unreacted DMP and related byproducts, followed finally by concentration. We were delighted that these efforts provided **1** in very high yield and purity (94%—quantitative, ca. ⩾95% purity—^{1}H and

* Corresponding author at present address: Hawai'i Pacific University, 45-045 Kamehameha Hwy, Kaneohe, HI 96744, United States. Tel.: +1 (808) 236 3551.
E-mail address: gberger@hpu.edu (G.O. Berger).
† Undergraduate or recent graduate/post baccalaureate researcher.

http://dx.doi.org/10.1016/j.tetlet.2014.11.100
0040-4039/

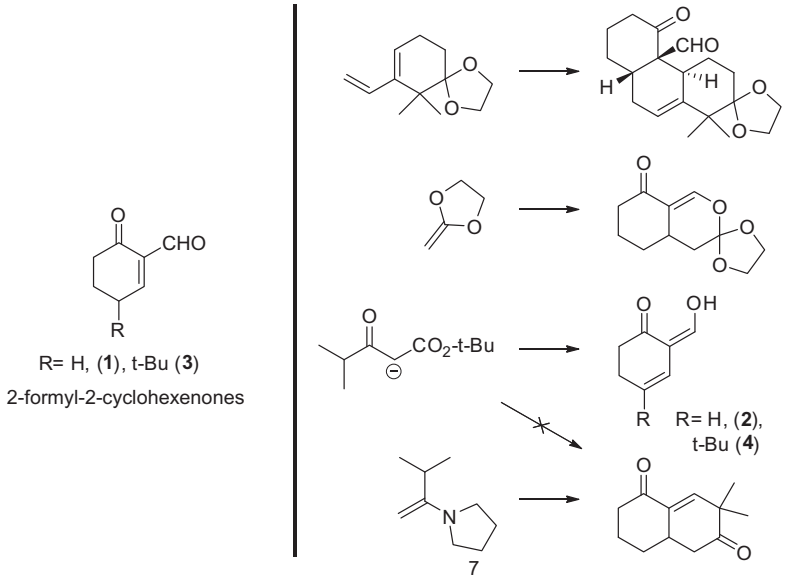
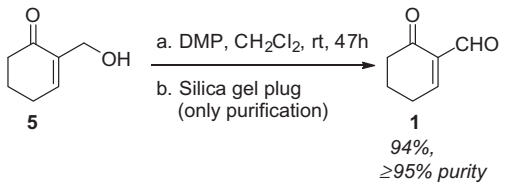


Figure 1. Representative uses and reactivity of 2-formyl-2-cyclohexanone.

^{13}C NMR). We were further pleased that the preparation was reliable and scalable (demonstrated on 30 mmol scale) (Scheme 1).

Next we sought to investigate the feasibility of conducting traditional types of Michael additions with **1**, similar to those reported as unsuccessful by Meyer, without having to resort to the enamine alternative which would not be applicable for our desired nucleophile, dimethylmalonate. Through a modest screen of conditions we were again delighted to find that at 0 °C the potassium enolate of dimethyl malonate added to **1** at C3 (1,4-addition) as expected, to produce the 2-(hydroxymethylenecyclohexanone adduct **6** in 60% yield (see Table 1, entry a). As with the preparation of **1**, we have been able to scale this reaction, to date up to 12.6 mmol with comparable yields. The primary impurity in the final crude material is residual dimethyl malonate that is slowly evaporated under reduced pressure over the span of approximately 1 week.[9] This reaction is very clean and we have used **6** either following flash chromatography, after filtration through a short plug of silica gel, or in crude form (following evaporative removal of malonate), in a subsequent protection step with comparable results. Our success may in part be a consequence of the high purity of **1**. Though there are other obvious differences between the conditions presented here (K^+ enolate/ether solvents) and that of Meyer (Na^+ enolate/DMSO or benzene solvent) it is somewhat surprising that we met with such early and repeated success where in the Meyer work there was essentially none unless the substrate was γ,γ-disubstituted. In general, we found that the conditions described were better than the common *soft enolization* methods (e.g., Li^+, R_3N) frequently used in Michael reactions and that a fast reaction at 0 °C was better than a slower one conducted at lower temperatures. As noted by others we have also found that **1** does not store well and should be used immediately. Having secured a supply of **1** we sought to determine the scope of the reaction with



Scheme 1. Dess–Martin preparation of 2-formyl-2-cyclohexanone.

Table 1
Traditional Michael reactions and other nucleophilic additions with 2-formyl-2-cyclohexanone

Entry	Conditions	Product
a	a. H_3CO_2C CO_2CH_3, KOtBu, THF; b. **1**, 0 °C, 15 min	**6** 60%
b	a. NC CN, KOtBu, THF; b. **1**, 0 °C, 1h	**7** 80% - Quant.
c	a. H_3CO CH_3, LDA, ether, -78 °C; b. **1**, 1h	**8** 44%
d	CH_3MgBr, ether, -78 °C, 1h	**9** 33%
e	a. H_3CO_2C $C(O)CH_3$, KOtBu, THF; b. **1**, 0 °C, 50 min	**10** 58%
f	a. CH_3NO_2, KOtBu, THF; b. **1**, 0 °C, 15 min	**11** 52%