Published in final edited form as:

Tetrahedron Lett. 2015 January 8; 56(2): 386–389. doi:10.1016/j.tetlet.2014.11.100.

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[†], and Gideon O. Berger^{*}

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

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.

Keywords

2-formyl-2-cyclohexenone; 2-formyl-2-cycloalkenone; Michael Addition; dimethylmalonate; conjugate addition

Introduction

2-formyl-2-cyclohexenone (**1**) has enjoyed a variety of important applications in synthesis (Figure 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 dienophile¹ 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.

© 2014 Elsevier Ltd. All rights reserved.

^{*}Gideon Berger, Hawai'i Pacific University, 45-045 Kamehameha Hwy, Kaneohe, HI 96744, (808) 236-3551, gberger@hpu.edu.

[†]Undergraduate or recent graduate/post baccalaureate researcher

Supporting Information Available: General methods and experimental procedures for the preparation of **1**, **6–11**, **13**, **14**, **16**, and **17** as well as reproductions of ¹H and ¹³C NMR data.

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.^{3,5,6,7} 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 form aldehyde 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 by products, followed finally by concentration. We were delighted that these efforts provided **1** in very high yield and purity (94% - quantitative, ca. 95% purity - ¹H & ¹³C NMR). We were further pleased that the preparation was reliable and scalable (demonstrated on 30 mmol scale).

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⁺, R₃N) 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 other nucleophile types. Multiple conditions were screened and optimized for each reaction type.

Malononitrile added to **1** leading to the highest yield in a clean reaction. The crude yield is reported here since product **7** could not be purified chromatographically due to further degradation (entry b). Nucleophiles that usually add in a 1,4 fashion did so here. Conversely and predictably the lithium enolate of methyl acetate added to the aldehyde carbonyl group to provide **8** in fair yield (entry c).¹⁰ Somewhat surprisingly, methyl Grignard added 1,4 providing **9**, though in poor yield (entry d). Interestingly, product **10** resulting from methylacetoacetate addition was isolated as the hydroxydihydropyran as mixture of two major diastereomers (~2:1, entry e).

In an effort to demonstrate the application of our approach to the preparation of other 2-formyl-2-cycloalkanones and their subsequent Michael Additions, we examined the reactions of **12** and **15**, both of which were prepared via Baylis-Hillman reactions (Scheme 2).¹¹ Oxidation followed by quick filtration provided 5- and 7-membered 2-formyl enones **13** and **16**, respectively, in excellent yield and purity. The Michael adduct derived from **13** decomposed during chromatography, therefore the enol was trapped as the ethyl ether to provide **14** in 20% yield over two steps (unoptimized). The Michael addition to **16** was also successful providing adduct **17** in modest yield. Interestingly γ -enolization, as described by Meyer, apparently represents a significant reaction pathway for **16**, since **18** was identified in the reaction mixture.

Finally, compounds **6**, **7**, **9**, **11** & **17** present some interesting spectral properties worthy of discussion. These compounds are all β -ketoaldehydes which are most commonly represented in the literature as the 2-(hydroxymethylene) cycloalkanones (enolized aldehyde). However, the ¹³C NMR shifts for **6** seem to be more indicative of a substituted 2-hydroxycyclohex-1-enecarbaldehyde and this is in agreement with predicted values (Table 2).¹² Strangely, weak coupling is observed between the O-H and H7, suggesting the cycloalkanone. We believe that this can be explained by the occurrence of a rapid equilibrium of the two forms, faster than the NMR timescale at room temperature, and favoring the 2-hydroxycyclohex-1-enecarbaldehyde structure. NMR spectra would then be weighted averages of the two forms present. This is supported by HMBC data which shows a strong correlation between the O-H and C1, C2 & C6 with a weaker correlation to C7. While the ¹³C shifts and these strong HMBC correlations indicate the enecarbaldehyde form of **6**, the weaker correlation to C7 as well as the proton coupling cannot readily be explained without the presence of the cycloalkanone as a minor constituent. Compounds **7**, **9** & **11** all display very similar ¹³C shifts to **6**, again suggesting that the carbaldehyde structure predominates.¹³ In contrast, the ¹³C shifts of **17** are indicative of cycloalkanone form. The predicted ¹³C shifts supports the cycloalkanone structure. The strong coupling observed between the O-H and H8 and the strong HMBC correlations between the O-H and C8, C2 provides confirmation of the cycloalkanone structure. Notably, there is the presence of a weaker HMBC correlation between the O-H and C1, C7 again suggesting that the carbaldehyde form of **17** is present in equilibrium but as a minor component. Interestingly, unsubstituted 2-hydroxycyclohex-1-enecarbaldehyde itself is almost always represented in the literature in the cycloalkanone form,¹⁴ however, the ¹³C shifts that have been reported are very similar to those of **6** and we

suspect that the carbaldehyde form is more accurate. On the other hand, the ^{13}C shifts reported for the unsubstituted 2-(hydroxymethylene) cycloheptanone are indeed consistent with that form.

Summary and Conclusions

We have developed robust and reliable conditions for the preparation of 2-formyl-2-cyclohexenone. Our route is cost effective since DMP can be prepared cheaply.¹⁵ We have also shown that, given a good source of the corresponding 2-(hydroxymethyl)-2-cycloalkenone, this is an excellent general method of preparing 2-formyl-2-cycloalkenones. Also, we have demonstrated that highly pure 2-formyl-2-cyclohexenone can be reliably used for many Michael additions as well as other nucleophilic additions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acknowledgement is made to the National Institute of General Medical Sciences, National Institutes of Health for generous support (P20GM 103466). We wish to sincerely thank Professor Marcus Tius and Professor Paul Helquist for their generous guidance and mentoring. We also wish to thank Wesley Yoshida for providing various 2D NMR, Casey Philbin, Professor Philip Williams and Hannah Tsunemoto for providing HRMS data and to Professor F. David Horgen for useful spectroscopy discussions.

References

1. Jung ME, Lui RM. J. Org. Chem. 1987; 75:7146. [PubMed: 20873743]
2. Hayes R, Li K-D, Leeming P, Wallace TW, Williams RC. Tetrahedron. 1999; 55:12907.
3. Meyer WL, Brannon MJ, Burgos C. da G, Goodwin TE, Howard RW. J. Org. Chem. 1985; 50:438.
4. Meyer WL, Brannon MJ, Merritt A, Seebach D. Tetrahedron Lett. 1986; 27:1449.
5. Liotta D, Barnum C, Puleo R, Zima G, Bayer C, Kezar HS III. J. Org. Chem. 1981; 46:2920.
6. Liu XL, Wang XC, Sheng SR, Huang X. Chin. J. Chem. 2004; 15:1009.
7. Sheng SR, Zhou W, Liu XL. J. Chem. Research. 2003:552.
8. Rezgui F, El Gaied MM. Tetrahedron. Lett. 1998; 39:5965.
9. The presence of residual dimethyl malonate can be conveniently monitored by ^1H NMR in C_6D_6 .
10. The 1,4 adduct was observed as a minor product. We had speculated that this might be the primary product given the, *double activation* of the C3 position of **1**.
11. In our hands the Baylis-Hillman preparations of both these materials was low yielding, particularly with the 7-membered ring adduct. However, we suspect that both of these reactions can be optimized.
12. Predicted values were generated using Chem Bio Draw Ultra[®] 12.0
13. An HMBC was run on compound **11** and showed the same correlation pattern as was the case with **6**.
14. Banwell MG, Ma X, Willis AC. Org. Prep. Proc. Int. 2005; 37:93.
15. Ireland RE, Liu L. J. Org. Chem. 1993; 58:2899.

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

Scheme 1.

Dess-Martin Preparation of 2-formyl-2-cyclohexenone.

Scheme 2.

Extension of methodology to 5 and 7 membered ring variants.

Table 1

Traditional Michael reactions and other nucleophilic additions with 2-formyl-2-cyclohexenone.

a)	1	a. $\text{H}_3\text{CO}_2\text{C}-\text{CH}_2-\text{CO}_2\text{CH}_3$ $\xrightarrow{\text{KOtBu, THF}}$ b. 1 , 0 °C, 15 min	6 60%
b)	1	a. $\text{NC}-\text{CH}_2-\text{CN}$ $\xrightarrow{\text{KOtBu, THF}}$ b. 1 , 0 °C, 1h	7 80% - Quant.
c)	1	a. $\text{H}_3\text{CO}-\text{C}(=\text{O})-\text{CH}_3$ $\xrightarrow{\text{LDA, ether, -78 } ^\circ\text{C}}$ b. 1 , 1h	8 44%
d)	1	$\xrightarrow{\text{CH}_3\text{MgBr}}$ ether, -78 °C, 1h	9 33%
e)	1	a. $\text{H}_3\text{CO}_2\text{C}-\text{CH}_2-\text{C}(=\text{O})\text{CH}_3$ $\xrightarrow{\text{KOtBu, THF}}$ b. 1 , 0 °C, 50 min	10 58%
f)	1	a. CH_3NO_2 , $\xrightarrow{\text{KOtBu, THF}}$ b. 1 , 0 °C, 15 min	11 52%

Table 2

Spectral features supporting either ketone or aldehyde form.

Strong HMBC Correlation to O-H :	C1, C2, C6
Weak HMBC Correlation to O-H :	C7
Predicted ¹³C Shifts (ppm) :	192(C1), 193(C7), 119(C2)
Observed ¹³C Shifts (ppm) :	187(C1), 187(C7), 110(C2)
O-H Coupling (Hz) :	3.7 (H7)