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# Regioselective 1,6-conjugate addition of organocuprate reagents to $\gamma$ -alkylidenebutenolides

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## ABSTRACT

This work describes the study of behavior of the  $\delta$ -substituted and  $\delta$ -non-substituted *exo*-cyclic double bond of  $\gamma$ -alkylidenebutenolides with dialkylcuprates. The addition reaction was found to be regioselective to afford the 1,6-conjugate adduct up to 87% yield.

1,4- and 1,6-conjugate addition reactions of carbon nucleophiles to electron-deficient alkenes represents a powerful tool for the formation of carbon-carbon bonds and more interestingly for the creation of tertiary or quaternary carbon stereocenters [1]. Due to the poor propagation of the electronic effect through the  $\pi$ -conjugated system (lower reactivity of the  $\delta$ -position as compared to the  $\beta$ -position), the regioselectivity of the 1,6-conjugate addition reactions is a real challenge to overcome. In addition,  $\gamma$ -alkylidenebutenolides **1** are an important class of naturally occurring  $\gamma$ -lactones endowing with diverse biological properties including herbicidal, antimicrobial, antitumor, antidiabetic and much more [2]. Possessing an  $\alpha,\beta,\gamma,\delta$  unsaturated moiety, as well as a cyclic enol acetate, those  $\gamma$ -lactones are interesting building blocks useful in various synthetic applications [3] and more specifically for the study of the regioselectivity of the 1,6-conjugate addition reactions of organocuprate reagents. To the best of our knowledge, only one example was reported by J. Font and coll. [4]. Unfortunately, the regioselective addition of dimethyl- and dibutylcuprates onto protoanemonine, the simplest  $\gamma$ -alkylidenebutenolide (**1** ( $R^1 = R^2 = R^3 = H$ )), proceeded with moderate yields, 27 and 17% respectively. Herein, we wish to report our study on the behavior of the  $\delta$ -substituted and  $\delta$ -non-substituted *exo*-cyclic double bond of  $\gamma$ -alkylidenebutenolides **1** with dialkylcuprates. (Scheme 1).

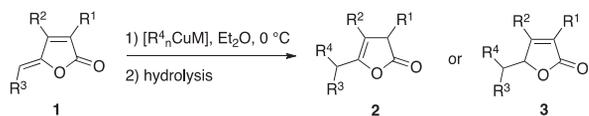
Our initial plan was to use  $\gamma$ -alkylidenebutenolide **1a** ( $R^1 = H$ ,  $R^2 = Me$ ,  $R^3 = Bu$ ) as a model substrate. **1a**, as well as the requisite

$\gamma$ -lactones **1**, were prepared according to our reported procedure [5]. The reaction was initially performed with 1.5 equivalent of  $Me_2CuLi\cdot LiI$  at 0 °C followed by a saturated aqueous  $NH_4Cl$  hydrolysis (Table 1, entry 1). In these conditions, we were delighted to observe that the reaction proceeded in a complete regioselective way. The 1,6-conjugate adduct **2a** was obtained in good yield (87%) after the selective  $\alpha$ -protonation of the corresponding lithium enolate intermediate.

Quenching the reaction with a buffer solution ( $NH_4Cl/NH_4OH$ ) at 0 °C or at -78 °C (Table 1, entries 2-3) didn't improve the isolated yield of **2a**.

In addition, no better results (Table 1, entries 4-5) were observed when the reaction was carried out neither with organocopper reagent  $MeCu\cdot LiI$  nor with higher-order cyanocuprate reagent  $Me_2CuLi\cdot LiCN$ .

Under the optimal reaction conditions, the scope of 1,6-conjugate addition was then assessed through the variation of the dialkylcuprate reagents ( $Me_2CuLi\cdot LiI$ ,  $Et_2CuMg\cdot MgI$  and  $Bu_2CuLi\cdot LiI$ ) and the nature of the substituents  $R^1$  (Me, H),  $R^2$  (Me, H) and  $R^3$  (Bu, H, Ph,  $CH_2OTBS$  and  $CH_2OMe$ ) onto the  $\gamma$ -alkylidenebutenolide **1** (Table 2). The methodology was found to be



**Scheme 1.** Regioselective 1,6-conjugate addition of organocuprate reagents to  $\gamma$ -alkylidenebutenolides **1**.

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**Table 1**  
Optimization of reaction conditions.

Entry	Me <sub>n</sub> CuM-LiX	hydrolysis	2a/3a/4a	Yield 2a
1	Me <sub>2</sub> CuLi-LiI	NH <sub>4</sub> Cl, 0 °C	1/0/0	87%
2	Me <sub>2</sub> CuLi-LiI	NH <sub>4</sub> Cl/NH <sub>4</sub> OH (9/1) 0 °C	1/0/0	66%
3	Me <sub>2</sub> CuLi-LiI	NH <sub>4</sub> Cl/NH <sub>4</sub> OH (9/1) -78 °C	1/0/0	86%
4	MeCu-LiI	NH <sub>4</sub> Cl, 0 °C	No reaction	
5	Me <sub>2</sub> CuLi-LiCN	NH <sub>4</sub> Cl, 0 °C	1/0/0	52%

**Table 2**  
Scope and Limit of the regioselective 1,6-conjugate addition of organocuprate reagents to  $\gamma$ -alkylidenebutenolides **1**.

Entry	1	R <sub>2</sub> <sup>3</sup> CuM-MX	2/3/4 <sup>a</sup>	Major Product	Yield
1		Me <sub>2</sub> CuLi-LiI	1/0/0		87%
2		Bu <sub>2</sub> CuLi-LiI	1/0/0		81%
3		Et <sub>2</sub> CuMg-MgI	1/0/0		66%
4		Me <sub>2</sub> CuLi-LiI	1/0/0		62%
5		Bu <sub>2</sub> CuLi-LiI	1/0/0		47%
6		Et <sub>2</sub> CuMg-MgI	1/0/0		39%
7		Me <sub>2</sub> CuLi-LiI	0/1/0		60% d.r. = 2:1
8		Me <sub>2</sub> CuLi-LiI	1/0/0		78%
9		Me <sub>2</sub> CuLi-LiI	1/0/0		46%
10		Me <sub>2</sub> CuLi-LiI	1/0/0		54%
11		Me <sub>2</sub> CuLi-LiI	0/1/0		52%
12		Bu <sub>2</sub> CuLi-LiI	0/1/0		41%
13		Me <sub>2</sub> CuLi-LiI <sup>b</sup>	7/93/0		56% d.r. = 7:3

<sup>a</sup> Ratio calculated from crude <sup>1</sup>H NMR.

<sup>b</sup> 2 equiv. of TMSCl were used as additive.

general with an excellent control of the regioselectivity of the conjugate addition affording the desired 1,6-adducts. When R<sup>2</sup> = Me and R<sup>3</sup> = Bu or CH<sub>2</sub>OTBS (Table 2, entries 1–6), the deconjugated  $\gamma$ -lactones **2a** were isolated in acceptable to good yields whatever the nature of the dialkylcuprates. The moderate yield (Table 2, entry 6) of the isolated **2b-Et** could be explained by its degradation during the purification step.

Indeed, unidentified compounds, which were non-present in the crude of the reaction, were isolated after the purification step. Interestingly, when R<sup>3</sup> = CH<sub>2</sub>OTBS is replaced by R<sup>3</sup> = CH<sub>2</sub>OMe (entry 7), the regioselective 1,6-conjugate addition still occurred

but with the formation of the conjugated  $\gamma$ -lactone **3c-Me** (60%), as a 2/1 mixture of two diastereomers, after the selective  $\gamma$ -protonation of the corresponding lithium enolate intermediate.

The regioselectivity was then assessed by using non- $\beta$ -substituted  $\gamma$ -alkylidenebutenolides **1d-1f** (Table 2, entries 8–10). When **1d** and **1e** were subjected to 1.5 eq. of Me<sub>2</sub>CuLi-LiI, we were delighted to observe a total regioselective 1,6-conjugate addition in satisfactory yields. This selectivity was also observed starting from the all conjugated  $\gamma$ -alkylidenebutenolide **1f** bearing a phenyl group (R<sup>2</sup> = H, R<sup>3</sup> = Ph) at the  $\gamma$ -position and promoting the 1,4-addition. Pleasantly, only the 1,6-adduct **2f-Me** was formed

(entry 10) without observing the presence of the other regioisomer arising from the 1,4-conjugate addition. In addition, starting from non- $\delta$ -substituted  $\gamma$ -alkylidenebutenolide **1h** (Table 2, entries 11–12), the regioselective 1,6-conjugate addition of  $\text{Me}_2\text{CuLi}\cdot\text{LiI}$  and  $\text{Bu}_2\text{CuLi}\cdot\text{LiI}$  occurred to give after purification, the conjugated  $\gamma$ -lactones **3g-Me** and **3g-Bu** in 52 and 41% yield respectively.

Finally, the 1,6-conjugate addition of  $\text{Me}_2\text{CuLi}\cdot\text{LiI}$  to  $\gamma$ -alkylidenebutenolide **1a** was then performed by using 2 eq. of chlorotrimethylsilane as additive [6]. Unfortunately, these conditions did not increase the yield of the reaction but, interestingly, allow us to mainly obtain, in moderate yield, the conjugated  $\gamma$ -lactone **3a-Me**, as a 7:3 mixture of 2 diastereomers, instead the deconjugated  $\gamma$ -lactones **2** (Table 2, entries 13). With these conditions in hand, we have a tunable 1,6-conjugate addition towards either deconjugated  $\gamma$ -lactones **2** or conjugated  $\gamma$ -lactones **3** starting from  $\beta$ -substituted  $\gamma$ -alkylidenebutenolides.

In conclusion, the conjugate addition of dialkylcuprate onto  $\delta$ -substituted  $\gamma$ -alkylidenebutenolides is described. This addition was found to be highly regioselective to afford the corresponding 1,6-conjugate adduct.

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