

Expedient Synthesis of Complex γ-Butyrolactones from 5-(1-Arylalkylidene) Meldrum's Acids via Sequential Conjugate Alkynylation/Ag(I)-Catalyzed Lactonization

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Supporting Information

ABSTRACT: The conjugate alkynylation of alkylidene Meldrum's acids with alkynylalanes and alkynyl Grignards allows for the formation of propargylic all-carbon quaternary stereocenters in high yields. Ag_2CO_3 -catalyzed intramolecular cyclization of propargylic Meldrum's acid derivatives offers a two-step entry into complex γ -alkylidene butyrolactones containing an all-carbon quaternary center at the C-4 position.

espite recent advances in the formation of all-carbon quaternary centers bearing alkyl and/or alkenyl groups through conjugate addition,¹⁻³ the number of analogous methods for the formation of propargylic all-carbon quaternary centers remains limited. Strategies employed to achieve 1,4regioselectivity in the conjugate addition of alkyl or alkenyl groups to α , β -unsaturated carbonyl compounds, such as the use of Cu(I) salts, has been hindered by the inertness of the Cu-C(sp) bond.⁴ Since the first report on the conjugate alkynylation of α,β -ketones by Hooz and Layton,⁵ synthetic chemists have addressed the chemo- and regioselective transfer of alkynes to electron-deficient olefins on several different fronts. Highly electrophilic reagents such as alkynylboranes and alkynylalanes have been utilized.^{6,7} Alkynylalanes have been shown to add to acyclic⁴ and cyclic enones, where the latter requires special conditions to overcome the unreactive nature of the s-trans conformation. For these acceptors, either an adjacent hydroxyl-directing group^{7c} or a transition metal catalyst^{7b} was required to allow for the conjugate addition. More recently, enantioselective conjugate alkynylations to $\alpha_{,\beta}$ unsaturated ketones for the formation of tertiary propargylic centers have been disclosed.^{6a,7a,8}

Alternatively, highly electrophilic acceptors have also been employed in conjunction with transition metals in the presence of chiral catalysts to access enantioenriched adducts.⁹ Carreira^{10c} and Fillion^{10b} independently reported the use of alkylidene Meldrum's acid as excellent acceptors in the enantioselective Cu- and Rh-catalyzed conjugate alkynylation reactions, respectively. Cui and Walker^{10a} also reported the conjugate addition of Zn-alkynylides in the presence of a chiral amino alcohol to Meldrum's acid alkylidenes. Moderate to high yields and enantioselectivities were achieved in the formation of tertiary carbon centers in each of these methods. Propargylic all-carbon quaternary centers have been prepared by Alexakis' group via the enantioselective copper-catalyzed 1,4-addition of alkyl Grignards to cyclic enynones.^{2c,11} As well, Hoveyda's



Ag₂CO₃ (cat.)

PhH/R⁴OH

However, to date and to the best of our knowledge, no general 1,4-conjugate alkynylation strategy for the formation of propargylic all-carbon quaternary centers has been reported. Herein, we present two general complementary methods for the 1,4-conjugate alkynylation of alkylidene Meldrum's acid derivatives 1 using either dimethyl aluminum or Grignard alkynylides (Scheme 1). Adducts 2 were readily transformed to highly functionalized γ -butyrolactones 3 by Ag(I)-catalyzed cyclization (Scheme 1).



M = MgCl, AlMe



Initial attempts to add Li-alkynylides to **1a** resulted in nearly quantitative recovery of starting material (<5% yield). We postulate that the higher basicity of the Li-alkynylides leads to γ -deprotonation at the methyl position resulting in isolation of starting material **1a** upon aqueous workup. On the other hand, the analogous Grignard reagent gave the desired 1,4-adduct. After optimization of reaction conditions two complementary protocols were developed (Table 1).¹³ The electronic character

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entry	alkylidene (R ¹ /R ²)	product (R ³)	$\begin{array}{c} \text{AlMe}_{2^{\prime}}^{a}\\ \text{MgCl}^{a,b}\\ (\%) \end{array}$ yield	
1	Ph/Me (1a)	TMS (2a)	83	85
2	4-MeC ₆ H ₄ /Me (1b)	TMS (2b)	77	82
3	4-(MeO)C ₆ H ₄ /Me (1c)	TMS (2c)	91	92
4	4-ClC ₆ H ₄ /Me (1d)	TMS (2d)	85	83
5	$4 - FC_6 H_4 / Me$ (1e)	TMS (2e)	75	84
6	$4-(F_3C)C_6H_4/Me$ (1f)	TMS (2f)	88	89
7	3-MeC ₆ H ₄ /Me (1g)	TMS (2g)	82	85
8	3-(MeO)C ₆ H ₄ /Me (1h)	TMS (2h)	84	76
9	2-ClC ₆ H ₄ /Me (1i)	TMS (2i)	NR	NR
10	2-(BnO)C ₆ H ₄ /Me (1j)	TMS (2j)	NR	NR
11	$2 - FC_6 H_4 / Me (1k)$	TMS (2k)	39	27
12	1-naphthyl/Me (11)	TMS (2l)	NR	NR
13	2-naphthyl/Me (1m)	TMS (2m)	76	84
14	2-furyl/Me (1n)	TMS (2n)	72	74
15	Ph/ <i>i</i> -Pr (10)	TMS (20)	66	83
16	Ph/c-Hex (1p)	TMS (2p)	64	77
17	Ph/cyclopropyl (1q)	TMS (2q)	69	81
18	Ph/CO_2Me (1r)	TMS $(2r)$	94	92
19	Ph/Me (1a)	H (2s)	N/A	86
20	Ph/Me (1a)	<i>n</i> -Bu (2t)	75	85
21	Ph/Me (1a)	Ph (2u)	77	81
22	Ph/Me (1a)	c-Hex (2v)	87	85
23	Ph/Me (1a)	$CH_2OH(2w)$	72 ^c	54 ^c
24	Ph/Me (1a)	$CH_2CH_2OH(2x)$	69 ^c	50 ^c
^a Isolated yield ^b THF as the solvent furnished comparable results $^{c}4$				

equiv were used.

of the aromatic group had no significant effect on the overall reactivity where both electron-withdrawing and -donating substituents resulted in good to excellent yields (Table 1, entries 1–8). Detrimental effects were observed for ortho substituted derivatives (entries 9–10, 12). We had previously observed similar reactivity of ortho-substituted 5-(1-arylalkylidene) Meldrum's acids in our enantioselective conjugate alkylation protocol.^{2e} It is interesting to note that ortho substitution with the smaller fluorine atom 1k yielded the desired adduct 2k (entry 11), albeit in modest yields, suggesting that steric properties governed the overall efficiency of the reaction. The aromatic groups furyl and naphthyl were also well tolerated (entries 13–14).

Increasing the steric bulk of the alkyl moiety from Me to the *i*-Pr and *c*-Hex group resulted in lower yields for the alkynylalanes than for the alkynyl Grignards (Table 1, entries 15-17). Excellent yields were achieved with the aryl-ester group at the electrophilic center (Table 1, entry 18). Addition of alkynylide AlMe₂ led exclusively to the delivery of the alkyne moiety, and no Me transfer was observed in all cases.

Next the formation of indenylidene Meldrum's acid 5a-b were briefly examined and good yields were obtained for both methods, eqs 1 and 2.



The nucleophilic scope of metal alkynylides was also investigated (Table 1). Good yields were obtained for both alkyl- and aryl-substituted alkynylides (entries 19-22). Propargyl and homopropargyl alcohols were added in moderate to good yields without the need for protection (entries 23-24).

Next, the lactonization of adducts 2s-u was investigated, since the γ -butyrolactone structural motif is found throughout a vast number of naturally occurring products.¹⁴ Transitionmetal-catalyzed cyclization of acetylenic compounds offers a direct and attractive route to the formation of γ -butyrolactones.¹⁵ Ag(I), Au(I), and Au(III) salts were screened, where Ag₂CO₃ led to highly regio- and stereoselective cyclizations (Table 2).¹⁶ Ag(I) salts gave 5-exo-dig products in high yields. Propargylic Meldrum's acid 2s readily cyclized to afford yalkylidene butyrolactones containing an ester (3b) or carboxylic acid (3c) moiety adjacent to the stereogenic center (entries 3 and 4). Cyclization of alkyl- and aryl-substituted propargyl Medrum's acids, 2t and 2u respectively, were more sensitive to reaction conditions (entries 5-10). Regio- and stereoselective E-3d and E-3e isomers were isolated in a more polar and Lewis basic solvent such as THF (entries 5 and 7). In benzene, a less polar solvent, mixtures of E/Z isomers were isolated (entries 6 and 8). Compound 2u afforded product Z-3f exclusively in a solution of benzene and water as the cosolvent (entry 9). Transition-metal-catalyzed cyclization of some alkynoic acids have been reported to give a mixture of E/Z isomers,^{15b,c} and was rationalized by the authors to be a result of isomerization of the Z isomer.^{15c} Attempts to isomerize E-3e or Z-3f by subjecting these products to Ag-salts in their respective reaction conditions over 24 h did not lead to any isomerization. Similarly, subjecting a mixture of E/Z isomers to the same reaction conditions did not change the relative ratio of the isomers formed.¹⁷ These results suggest the possibility of competing pathways (Scheme 2). Path I accounts for the formation of the Z isomer, where anti- attack of the carbonyl-O onto the alkyne-coordinated Ag(I) complex gives rise to the 5exo-dig intermediate Ia. The E-isomer may result from a syncarbometalation of the carbonyl-O and ${\rm Ag}({\rm I})$ ion across the triple bond giving rise to the 5-exo-dig intermediate IIa. Thermally induced cycloreversion of Ia and IIa resulted in the formation of acylketene intermediates Ib and IIb respectively,¹⁸ followed by nucleophilic attack of the corresponding solvent affording the γ -alkylidene butyrolactone. Reactions ran in water at room temperature gave rise to the carboxylic acid γ alkylidene butyrolactone 3c. Compounds 2t and 2u subjected to identical reaction conditions gave mixtures of carboxylated and decarboxylated butyrolactones. However, upon gentle



^aIsolated yield. ^bReaction ran at 85 °C for 2 h. ^cReaction ran at rt for 18 h.

Scheme 2. γ-Alkylidene Butyrolactones Formation Mechanism



heating to 85 °C decarboxylated γ -alkylidene butyrolactones were exclusively formed (Table 2, entries 1, 5, and 9). Further evidence for the acylketene intermediate was observed when cyclization reactions were run in the absence of a nucleophilic solvent. No cyclized products were observed as a result of rapid decomposition of the unstable acylketene intermediate.^{3c}

In summary, the versatility of alkylidene Meldrum's acids as excellent acceptors in conjugate addition reactions has been expanded to give rise to propargylic all-carbon benzylic quaternary centers under mild reaction conditions. Two complementary practical protocols allow for the formation of a wide range of propargyl Meldrum's acid derivatives that can be readily converted to complex γ -alkylidene butyrolactones. These unprecedented butyrolactones display a stereogenic allcarbon quaternary center at the C-4 position. Current efforts center on developing enantioselective versions of these protocols.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of new compounds including NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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