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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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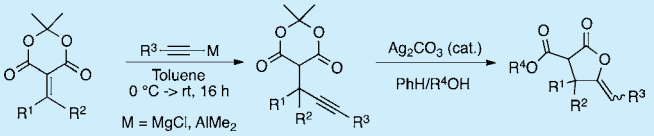
Supporting Information

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.

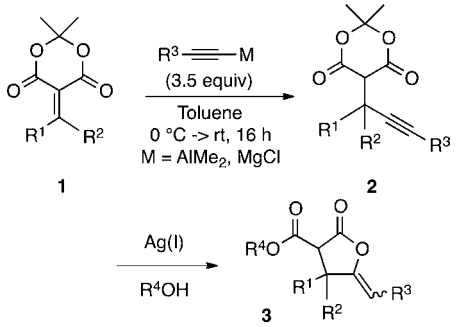


Despite recent advances in the formation of all-carbon quaternary centers bearing alkyl and/or alkenyl groups through conjugate addition,[1−3] the number of analogous methods for the formation of propargylic all-carbon quaternary centers remains limited. Strategies employed to achieve 1,4-regioselectivity 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 acyclic[4] 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 α,β-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 group has reported the S_N2' addition of alkynylalanes to allylic phosphates resulting in enantiopure 1,4-enynes adducts.[12]

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).

Scheme 1. General Strategy



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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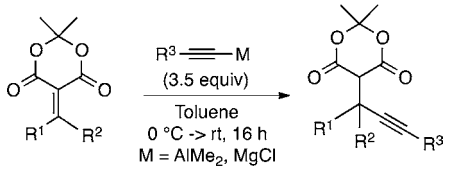
Table 1. Conjugate Addition of Metal Alkynylides to Alkylidene Meldrum's Acids 1a−r



1 2

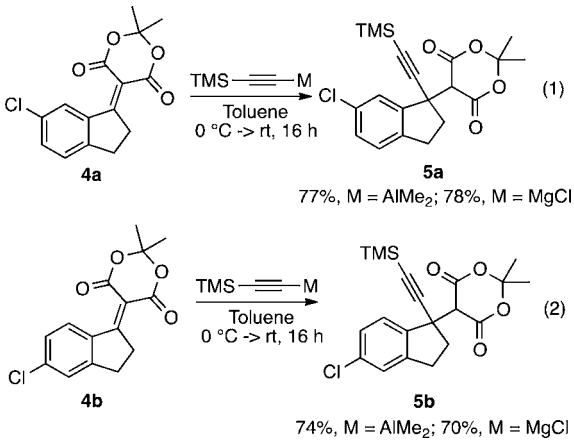
entry	alkylidene (R^1/R^2)	product (R^3)	$AlMe_2$,[a] $MgCl$[a,b] yield (%)	
1	Ph/Me (**1a**)	TMS (**2a**)	83	85
2	4-MeC_6H_4/Me (**1b**)	TMS (**2b**)	77	82
3	4-$(MeO)C_6H_4$/Me (**1c**)	TMS (**2c**)	91	92
4	4-ClC_6H_4/Me (**1d**)	TMS (**2d**)	85	83
5	4-FC_6H_4/Me (**1e**)	TMS (**2e**)	75	84
6	4-$(F_3C)C_6H_4$/Me (**1f**)	TMS (**2f**)	88	89
7	3-MeC_6H_4/Me (**1g**)	TMS (**2g**)	82	85
8	3-$(MeO)C_6H_4$/Me (**1h**)	TMS (**2h**)	84	76
9	2-ClC_6H_4/Me (**1i**)	TMS (**2i**)	NR	NR
10	2-$(BnO)C_6H_4$/Me (**1j**)	TMS (**2j**)	NR	NR
11	2-FC_6H_4/Me (**1k**)	TMS (**2k**)	39	27
12	1-naphthyl/Me (**1l**)	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*-Pr (**1o**)	TMS (**2o**)	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**)	*n*-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 $AlMe_2$ 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] Transition-metal-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 Ag_2CO_3 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 γ-alkylidene 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 5-*exo-dig* intermediate **Ia**. The *E*-isomer may result from a syn-carbometalation of the carbonyl-*O* and Ag(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

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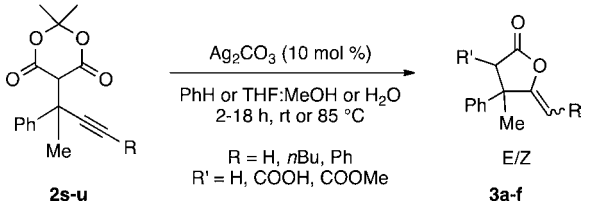
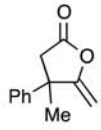
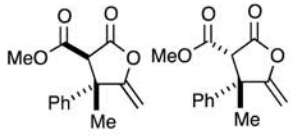
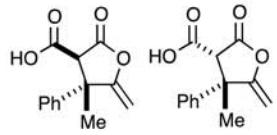
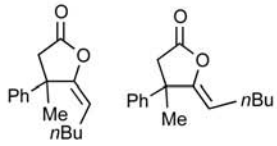
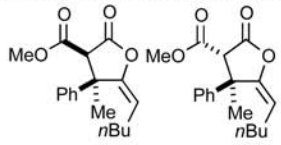
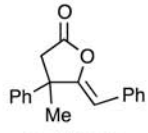
Table 2. Ag(I)-Catalyzed Formation of γ-Alkylidene Butyrolactones

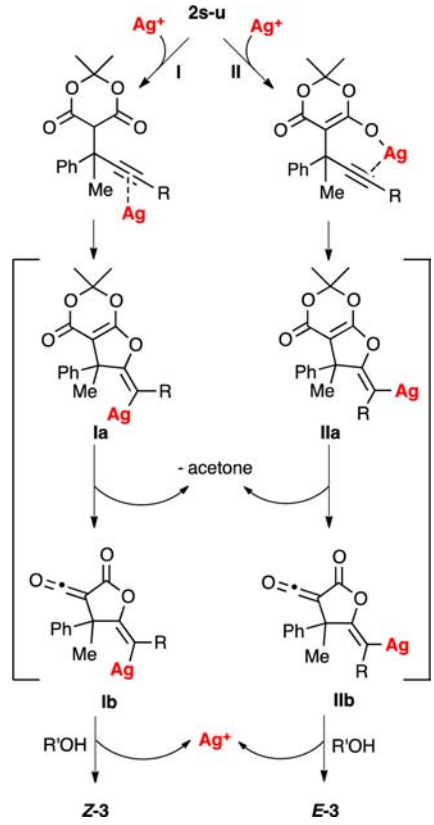


2s-u **3a-f**

entry	R	solvent	product (yield %)[a]
1	H (**2s**)	PhH:H$_2$O (10:1)	 **3a** (98)[b]
2	H (**2s**)	THF:H$_2$O (10:1)	**3a** (88)[b]
3	H (**2s**)	PhH:MeOH (10:1)	 **3b** (93)[b], 3:1 dr
4	H (**2s**)	PhH:H$_2$O (4:1)	 **3c** (88)[c], 3:1 dr
5	*n*Bu (**2t**)	THF:H$_2$O (10:1)	 **3d** (86)[b], 29:1 E/Z mixture
6	*n*Bu (**2t**)	PhH:H$_2$O (10:1)	**3d** (89)[b], 2:3 E/Z mixture
7	*n*Bu (**2t**)	THF:MeOH (4:1)	 ***E*-3e** (81)[b], 3:1 dr
8	*n*Bu (**2t**)	PhH:MeOH (10:1)	**3e** (79)[b], 2:1 E/Z mixture
9	Ph (**2u**)	PhH:H$_2$O (10:1)	 Z-**3f** (92)[b]
10	Ph (**2u**)	THF:H$_2$O (10:1)	**3f** (88)[b], 2:5 E/Z mixture

[a]Isolated yield. [b]Reaction ran at 85 °C for 2 h. [c]Reaction 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 all-carbon 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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(16) $AgNO_3$ gave the 5-*exo-dig* product but in lower yields. AuCl gave a varying mixture of the 5-*exo-dig* and 6-*endo-dig* products depending on reaction conditions. $AuCl_3$ resulted in the formation of complex mixtures.

(17) Determined by comparing the chemical shift of vinylic protons of γ-alkylidene butyrolactones. No change was observed in their crude ^{1}H NMR spectrum.

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