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$AgNO_3$ catalyzed cyclization of propargyl-Meldrum's acids in aqueous solvent: highly selective synthesis of *Z*-γ-alkylidene lactones

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ABSTRACT

γ-Alkylidene lactones have attracted considerable attention due to their diverse biological activities and ubiquitous structural units in natural products. Herein, an efficient $AgNO_3$ catalyzed highly regio- and stereo-selective cyclization of propargyl-Meldrum's acids in aqueous solvent was developed, which provides a practical synthetic strategy for the synthesis of substituted *Z*-γ-alkylidene butyrolactones under neutral reaction conditions.

γ-Alkylidene lactones are widely distributed in a vast array of natural bioactive molecules,[1,2] such as cyanobacterin,[2a] atranone,[2b] growth regulating reagent,[2c] and goniobutenolides[2d] (Fig. 1). Their enolester moiety makes them of great importance in the areas of pharmaceuticals. Many of these enolesters possess interesting and powerful biological properties such as anticancer,[3] anti-HIV,[4] and antibiotic and cytotoxic activity,[5] and therefore have been developed as drugs.

In the past decades, lots of useful synthetic methods have been developed for these γ-alkylidene lactones, among which, transition metals such as mercury,[6] palladium,[7] rhodium,[8] silver,[9,10] gold,[11] and copper[12] catalyzed cyclization reactions of acetylenic acids present one of the most attractive and straightforward synthetic approaches (Scheme 1). Despite their efficiencies, there are still some drawbacks: (1) All of the above transformations started from acetylenic acids, which required several synthetic steps from the corresponding propargyl malonic esters generating wasted from reagents, solvents, and purifications (Scheme 1); (2) base was required in most of these reactions; (3) furthermore, when Ag^+ salts were used as catalysts in these reactions, the reported literatures indicate that a dark environment was required for these reactions, and the stereoselectivity was low (*E*/*Z* isomers, 1:1).[9] Recently, the development of new synthetic methods through concise and economical routs has attracted a great deal of attention. Herein, we demonstrate a practical $AgNO_3$ catalyzed highly regio- and stereo-selective cyclization of propargyl-Meldrum's acids leading to substituted *Z*-γ-alkylidene butyrolactones in aqueous solvent under neutral reaction conditions (Scheme 1).

We have recently reported a novel Cu/Fe cocatalyzed highly selective tandem conjugate addition–cyclization–hydrolysis–decarboxylation reactions of alkynes and 5-alkylidene Meldrum's acids leading to substituted *Z*-γ-alkylidene butyrolactones.[13] Although this method overcame the above shortages by the tandem processes using easily prepared precursor of acetylenic acids as starting materials, the high loading of metal catalyst (40 mol %) limits its application, and leaves room for further improvement. Based on our above-mentioned results, we envisioned that a Lewis acid which is stable in water, could facilitate this transformation from propargyl-Meldrum's acids to substituted γ-alkylidene butyrolactones via cyclization–hydrolysis–decarboxylation[13] in an aqueous solvent.

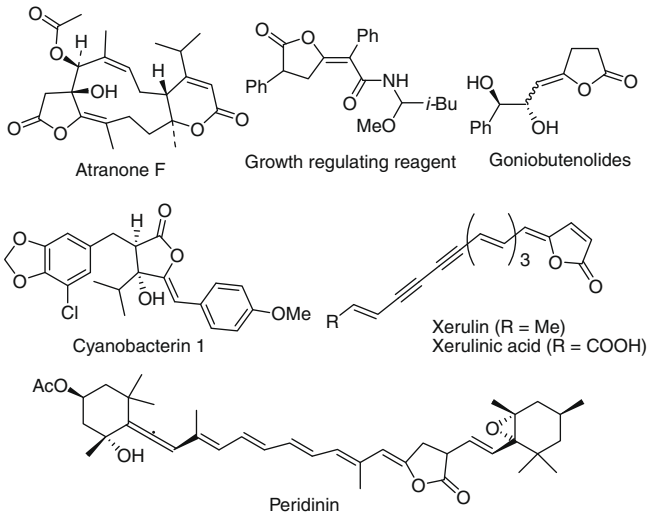

Figure 1. Selected examples of γ-alkylidene lactones frameworks.

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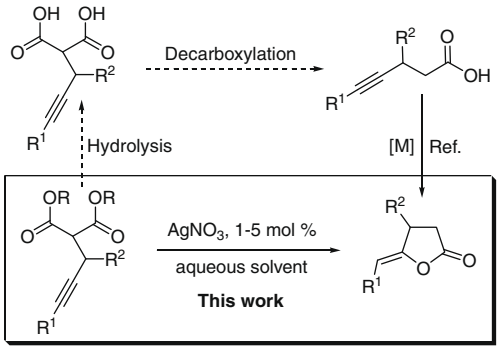


Scheme 1. Synthesis of substituted γ-alkylidene butyrolactones via transition metal-catalyzed reactions.

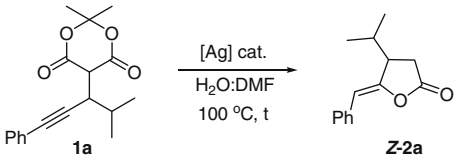
With this hypothesis in mind, after a great deal of screening, we are pleased to find that Ag_2CO_3 can smoothly complete this conversion starting from propargyl-Meldrum's acids **1a** highly regio- and stereo-selectively giving γ-alkylidene butyrolactones ***Z*-2a** in 71% yield, no ***E*-2a** was observed (Table 1, entry 4). Further studies indicated that the efficiency of this transformation was obviously affected by the ratio of the aqueous solvent (Table 1, cf. entries 2, 5, and 6). After screening on different silver catalysts and solvents, we found that the direct cyclization of propargyl-Meldrum's acids **1a** catalyzed by $AgNO_3$ (5 mol %) using the mixture of H_2O/DMF (2:1) as solvent at 100 °C led to the highest efficiency (87% yield, entry 7). Notably, 82% yield of ***Z*-2a** was obtained when only 1 mol % of $AgNO_3$ was employed as the catalyst (Table 1, entry 8).

Compared with the reported silver-catalyzed cyclization of acetylenic acids,[9] our approach uses propargyl-Meldrum's acids as starting materials, which is the precursor of the above-mentioned acetylenic acids. With our method, the reactions are carried out in aqueous solvent (H_2O/DMF = 2:1) under neutral reaction conditions, and are easily handled without the requirement of dark environment. Furthermore, the regio- and stereoselectivity are high leading to *Z*-γ-alkylidene butyrolactones.

Under these optimized conditions, the scope of this cyclization–hydrolysis–decarboxylation reaction was examined (Table 2). Various substituted propargyl-Meldrum's acids **1** proceeded efficiently producing ***Z*-2** in moderate to good yield. Aryl substituents with both electron withdrawing and electron donating at R^1 position participated well (Table 2, entries 2–5). It is noteworthy that 4-bromoaryl substituted product ***Z*-2e** was afforded in 85% yield, which could be amenable to further functional-group transformations. A wide range of substituents at R^2 position, such as alkyl, aryl, and heteroaryl groups, reacted successfully and yielded the expected 4-substituted *Z*-γ-alkylidene butylroactones, respectively (Table 2, 45–75%, entries 6–10).

In conclusion, we have developed a silver catalyzed efficient highly selective tandem cyclization–hydrolysis–decarboxylation of substituted propargyl-Meldrum's acids leading to ***Z*-γ-alkylidene butyrolactones.** Compared with the reported transition metal-catalyzed cyclization of acetylenic acids, propargyl-Meldrum's acids, which are the precursor of the above-mentioned acetylenic acids, are used as starting materials. This developed method is easily handled in aqueous solvent under neutral reaction conditions with low catalyst loading. Further studies on the synthetic applications are ongoing in our laboratory.

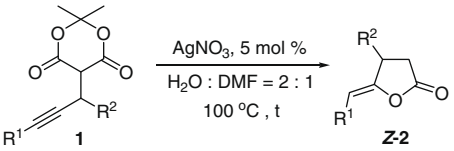
Table 1
The silver-catalyzed cyclization–hydrolysis–decarboxylation reaction of propargyl-Meldrum's acid **1a**[a]



Entry	[Ag] (mol %)	H_2O:DMF	*t* (min)	Yield of ***Z*-2a**[b] (%)
1	AgOAc (20)	2:1	40	65
2	$AgNO_3$ (20)	2:1	40	87
3	Ag_2O (10)	2:1	40	54
4	Ag_2CO_3 (10)	2:1	40	71
5	$AgNO_3$ (20)	4:1	50	52
6	$AgNO_3$ (20)	1:1	50	17
7	$AgNO_3$ (5)	2:1	40	87
8	$AgNO_3$ (1)	2:1	40	82

[a] **1a** (0.15 mmol), Ag salt, H_2O (1 mL) and DMF were added in the appropriate volume ratio and the mixture was allowed to react at 100 °C under air.
[b] Isolated yield.

Table 2
The silver-catalyzed cyclization–hydrolysis–decarboxylation reaction of substituted propargyl-Meldrum's acid **1**[a]



Entry	1	R_1	R_2	*t* (min)	Yield of ***Z*-2**[b] (%)
1	**1a**	Ph	^{i}Pr	40	87 (***Z*-2a**)
2	**1b**	4-Me-C_6H_4	^{i}Pr	60	71 (***Z*-2b**)
3	**1c**	4-F-C_6H_4	^{i}Pr	60	81 (***Z*-2c**)
4	**1d**	4-OMe-C_6H_4	^{i}Pr	50	46 (***Z*-2d**)
5	**1e**	4-Br-C_6H_4	^{i}Pr	50	85 (***Z*-2e**)
6	**1f**	Ph	4-Me-C_6H_4	50	62 (***Z*-2f**)
7	**1g**	Ph	Ph	50	63 (***Z*-2g**)
8	**1h**	Ph	Furfuryl	50	59 (***Z*-2h**)
9	**1i**	Ph	^{i}Bu	60	45 (***Z*-2i**)
10	**1j**	Ph	^{c}Hex	60	75 (***Z*-2j**)

[a] **1** (0.25 mmol), $AgNO_3$ (0.0125 mmol) and aqueous solvent (H_2O:DMF = 2:1, 1.5 mL) were allowed to react at 100 °C under air.
[b] Isolated yield.

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Supplementary data

Supplementary data (experimental details and NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.050.

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