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Synthesis of 3,4-disubstituted α-methylene-γ-lactones via sonochemical Barbier-type reaction

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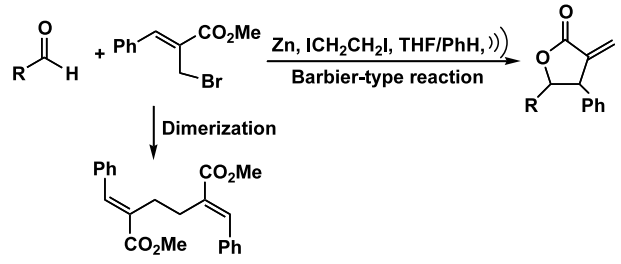
Abstract—A series of 3,4-disubstituted α-methylene-γ-lactones were synthesized by the addition reaction of allylic bromide with aldehyde via sonochemical Barbier-type reaction condition and then followed by the in situ intramolecular esterification. The α-methylene-γ-lactone was produced as the sole product when THF/PhH solvent mixture was used whereas the allylation adduct was generated as the major product when solvent DMF was used.

α-Methylene-γ-lactones are extensively occurrence in nature and display a variety of interesting biological activities such as antibacterial,[1,2] anticancer,[3–6] antimalarial,[7] inhibition of microbial growth,[8] plant growth[9] and both convulsant and anti-convulsant activity.[10] The α-methylene-γ-lactones have been received much attention as synthetic targets and have been widely reported in the literature.[11–20] The nucleophilic addition reaction of aldehyde with allylmetal (Cr,[21] Si,[22] Sn,[23,24] Sn/Al,[25] Zn[26]) and then followed by intramolecular cyclization is the simplest and the most direct method for the synthesis of α-methylene-γ-lactone. Unfortunately, 3,4-diaryl-α-methylene-γ-lactones can not be produced easily by this methodology due to the conjugation stability of 3-phenylallyl bromide in allylation reaction (Scheme 1).[21] Herewith, we wish to report the synthesis of 3,4-diaryl-α-methylene-γ-lactone by the addition reaction of 3-phenylallyl bromide to aldehyde via sonochemical Barbier-type reaction condition[27–29] and then followed by the in situ lactonization.



Scheme 1.

A typical procedure[30] for the synthesis of a 3,4-disubstituted α-methylene-γ-lactone is as follows: A solution of aldehyde (1.0 mmol) and allylic bromide (1.2 mmol) in anhydrous THF (1.0 mL) was added to a reaction mixture of zinc (5.0 mmol) and 1,2-diiodoethane[31] (1.0 mmol) in anhydrous THF/PhH (3.5 mL/0.5 mL) under sonication in a commercial ultrasonic cleaning bath[32] (Elma-T490DH, 50 kHz) for three hours at around 43°C. After the sonication, an aqueous 5% NH_4Cl (8.0 mL) was added and the filtrate was extracted with ether (3×20 mL). The combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, filtered, and then the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane as eluant.

A series of 3,4-disubstituted α-methylene-γ-lactones were synthesized under the reaction conditions and the results are shown in Table 1. All the 3,4-disubstituted α-methylene-γ-lactones were characterized by spectral analysis and by comparison with the authentic compounds. The better diastereoselectivity is achieved when both substituents are aromatic groups (Table 1, entries 4–9). Previous studies showed that some α-methylene-γ-lactones were produced by the allylation addition and then followed by lactonization which was afforded by the introduction of strong acid. Our experimental investigations showed that the reaction mixture of Zn and ICH_2CH_2I in THF/PhH became acidic solution (pH ~2) under sonication which in situ promoted lactonization. The experimental results also showed that both addition and lactonization process were completed even the reaction was quenched with water.

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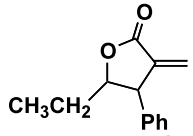
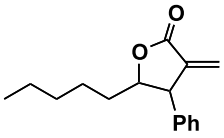
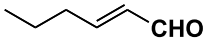
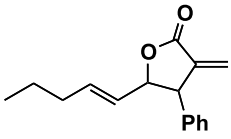
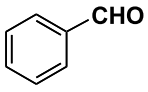
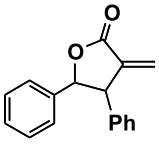
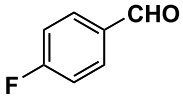
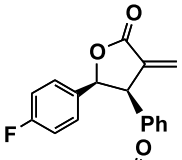
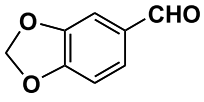
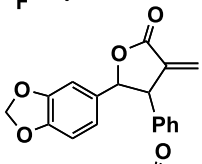
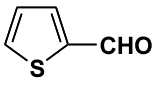
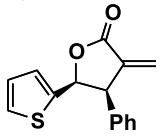
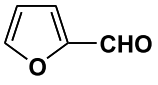
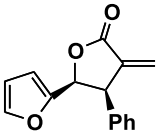
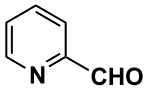
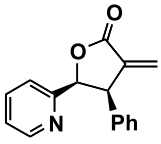
Table 1. Synthesis of 3,4-disubstituted α-methylene-γ-lactones

Entry	Aldehyde	γ-Lactone	Yield[a](*cis*/*trans*)[b]
1	CH_3CH_2-CHO		80% (86/14)
2	C_5H_{11}-CHO		39% (82/18)
3			67% (82/18)
4			63% (83/17)
5			43% (100/0)
6			48% (94/6)
7			48% (100/0)
8			51% (100/0)
9			84% (100/0)

(a). The yields were determined after chromatographic purification.
(b). The *cis*/*trans* ratios were determined by ^{1}H-NMR spectral analysis.

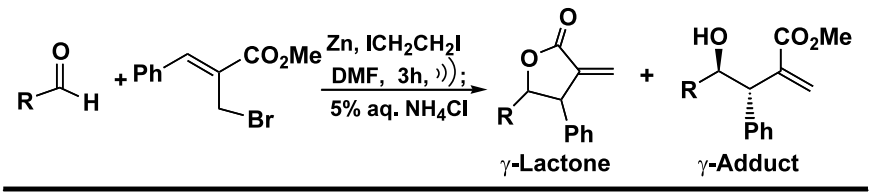
The choice of solvent exhibits tremendous impact in sonochemical Barbier-type reaction.[33,34] Thus, we investigated this Barbier-type reaction underwent in solvent DMF and the allylation product (γ-adduct) became the major product and the results are shown in Table 2.

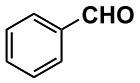
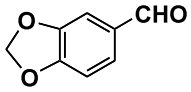
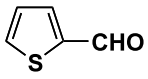
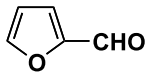
The combined yield of γ-lactone and γ-adduct is higher when the reaction was proceeded in DMF. The stereochemistry for the formation of γ-lactone is less selective in DMF. The formation of 2,3-diaryl-3-hydroxy ester (γ-adduct) is highly stereoselective and only *anti*-stereoisomer was obtained (Table 2, entries 3–6).

The heteroaryl substituted α-methylene-γ-lactones were potentially biologically active compounds. Therefore, we introduced this reaction condition for synthesis of 3,4-diheteroaryl-α-methylene-γ-lactones and the results are shown in Scheme 2.

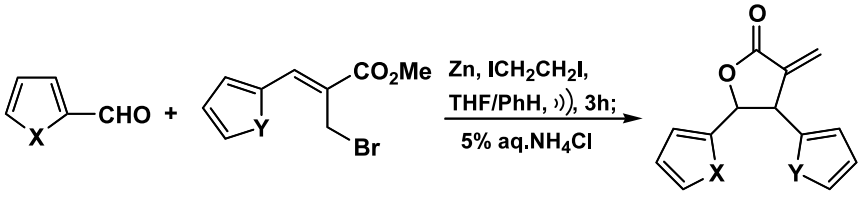
In conclusion, we demonstrate a simple and an efficient method for the synthesis of 3,4-disubstituted α-methylene-γ-lactone via sonochemical Barbier-type reaction condition. The 3,4-diaryl-α-methylene-γ-lactones were successfully synthesized and *cis*-stereoisomer was the major product under the reaction condition.

Table 2.



Entry	Aldehyde	γ-Lactone[a] (*cis*/*trans*)[b]	γ-Adduct[a] (*anti*/*syn*)[b]
1	Et-CHO	40% (56/44)	41% (63/37)
2	C_5H_{11}-CHO	24% (75/25)	35% (54/46)
3		27% (83/17)	41% (100/0)
4		19% (100/0)	44% (100/0)
5		20% (100/0)	53% (100/0)
6		trace	41% (100/0)

(a). The yields were dertermined after chromatographic purification.
(b). The stereochemistry was determined by ^{1}H-NMR spectral analysis.



X = O, Y= S — 68% (cis/trans = 95/5)
X = S, Y= S — 72% (cis/trans = 95/5)
X = O, Y= O — 71% (cis/trans = 56/44)
X = S, Y= O — 43% (cis/trans = 52/48)

Scheme 2.

Acknowledgements

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30. All reagents were purchased from Aldrich and Riedel-deHaen and all were used directly without further purification.
31. The ZnI_2 and ethene were generated form Zn powder and 1,2-diiodoethane under sonication.
32. The bath should be filled with water containing some 3–5% detergent. In our laboratory, we used Decon 90 which permits much more even cavitation in bath water.
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