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Synthesis of *cis*-3,4-diaryl α-methylene-γ-butyrolactams via sonochemical Barbier-type reaction

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ABSTRACT

A series of *cis*-3,4-diaryl α-methylene-γ-butyrolactams were synthesized by the addition reaction of 3-phenylallyl bromide with *N*-tosyl aldimine via sonochemical Barbier-type reaction condition and then followed by the in situ intramolecular amidation. The *cis*-3,4-diaryl α-methylene-γ-butyrolactam was obtained as the sole regio- and stereoisomeric product when *N*-tosyl aldimine was used as the substrate whereas the monoaryl α-methylene-γ-butyrolactam was also generated when *N*-phenyl aldimine was used.

α-Methylene-γ-butyrolactams[1–3] are interesting compounds from a biological point of view because they exhibit less cytotoxic activity than the corresponding α-methylene-γ-butyrolactones, making them display a variety of biological activities such as antibacterial,[4] anticancer,[5] antivirus,[6] kinase regulator[7], and inhibitor of proteasome.[8,9] Compared to α-methylene-γ-buryrolactones,[10] the preparation of the corresponding nitrogenated derivatives is the subject of a few reports in the literature. Allylation (Zn,[11–17] In[18]) and metal-promoted cyclization (Pd,[19] Rh,[20] B,[21]) as well as anionic[22–24] methodologies have been used to prepare α-methylene-γ-butyrolactams: one disadvantage of many of these procedures is that together with the expected compound the corresponding endocyclic unsaturated lactam is also generated, resulting from an undesired isomerization. Among them, the nucleophilic addition reaction of allylmetal with aldimine and then followed by intramolecular cyclization is the most direct method for the synthesis of 3,4-disubstituted α-methylene-γ-butyrolactam. However, 3,4-diaryl α-methylene-γ-butyrolactams cannot be produced easily by these methodologies due to the conjugation stability of 3-phenylallyl bromide in the allylation reaction[25] (Scheme 1). The addition of 3-substituted allylmetal to aldimine followed by intramolecular amidation may produce two types of α-methylene-γ-butyrolactams, α-adduct (monoaryl, S_N2 pathway) and γ-adduct (diaryl, S_N2' pathway). Our laboratory previously developed a simple and an efficient method for the synthesis of 3,4-disubstituted α-methylene-γ-butyrolactone[10] and we further employed this method for the preparation of α-methylene-γ-butyrolactam by the reaction of allylic bromide with aldimine. Herewith, we wish to report the synthesis of *cis*-3,4-diaryl-α-methylene-γ-butyrolactam by the addition reaction of 3-phenylallyl bromide to *N*-tosyl aldimine via sonochemical Barbier-type reaction condition.[26–28]

The first feasibility of our approach was first tested by adding a mixture of zinc (5.0 mmol) and 1,2-diiodoethane (1.0 mmol) to a THF solution of 3-phenylallyl bromide (1.2 mmol) and *N*-benzyl aldimine (1.0 mmol) and then the reaction mixture was sonicated for 3 h (Table 1). The expected product 3,4-diphenyl-α-methylene-γ-butyrolactam was only obtained with 4% and monoaryl γ-butyrolactam (α-adduct) was produced as the major product (15%). The stereochemistry of 3,4-diaryl-α-methylene-γ-butyrolactam and monoaryl γ-butyrolactam was determined and compared by ^{1}H-NMR spectra of the reported compounds.[11,22,24] The choice of N-substituent for aldimine may exhibit impact regioselectivity under allylation reaction. Thus, we investigated other aldimines such as *N*-*p*-methoxy and *N*-tosyl aldimines under this Barbier-type reaction conditions. The monoaryl γ-butyrolactam product was not observed when *N*-tosyl aldimine was introduced and the yield of 3,4-diphenyl-α-methylene-γ-butyrolactam increased dramatically to 72% (Table 1, entry 4). It is also worthy to know that only *cis*-stereoisomer was observed by comparison with the authentic compound. Previous studies showed that α-methylene-γ-lactams were produced by the allylation addition and then followed by amidation reaction which was afforded by introduction of a coupling reagent such as DCC (dicyclohexylcarbodiimide).[18] Our experimental results showed that regioselective and stereoselective allylation and consequently intramolecular amidation were all completed under the reaction condition without further introducing amidating agent. Our previous investigations showed that the reaction mixture of Zn and ICH_2CH_2I in THF became acidic solution (pH ~2) under sonication which may promote the following amidation reaction.[10,29]

To understand and expand the scope for the synthesis of 3,4-diaryl α-methylene-γ-butyrolactams by this Barbier-type reaction,

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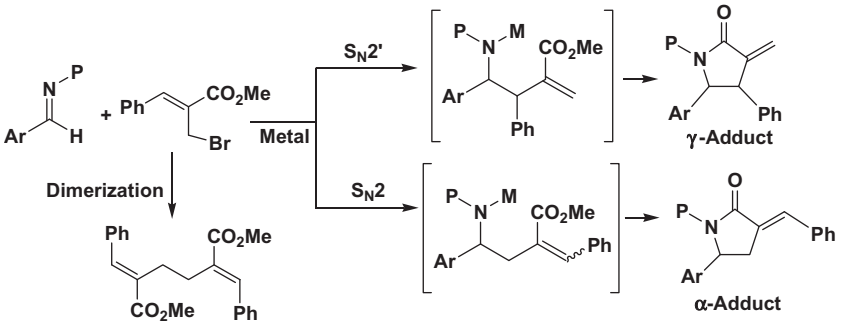
a series of *N*-tosyl aldimines was investigated and the results are shown in Table 2. The 3,4-diaryl α-methylene-γ-butyrolactams were obtained in all investigated cases and no α-adduct (monoaryl product) was observed under the reaction condition. The *cis*-diastereoselectivity is achieved and the stereochemistry was characterized by spectral analysis.

A representative procedure[30] for the synthesis of a *cis*-3,4-diaryl-α-methylene-γ-butyrolactam is as follows: a solution of *N*-tosyl aldimine (1.0 mmol) and 3-phenylallyl bromide (1.2 mmol) in anhydrous THF (1.0 mL) was added by cannula to a reaction mixture of zinc (5.0 mmol) and 1,2-diiodoethane[31] (1.0 mmol) in anhydrous THF (5 mL). The reaction mixture was sonicated in a commercial ultrasonic cleaning bath[32] (Elma-T490DH, 50 kHz) for 3 h at around 43 °C. After the sonication, an aqueous 5% NH_4Cl (8.0 mL) was added and the filtrate was extracted with ether (20 mL × 3). 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.

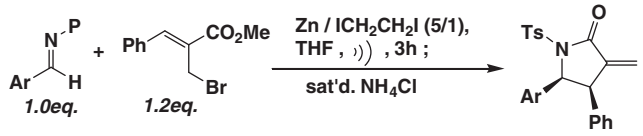
The experimental results showed that the formation yields of *cis*-3,4-diaryl α-methylene-γ-butyrolactams are moderate to high. All the *cis*-3,4-diaryl α-methylene-γ-butyrolactams were characterized by NMR and HRMS spectral analysis. The *cis*-diastereoselectivity is achieved in all investigated cases.

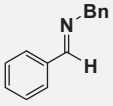
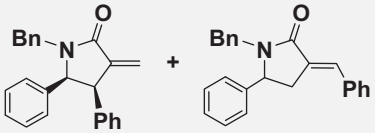
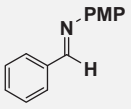
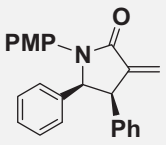
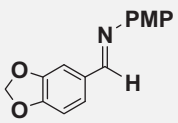
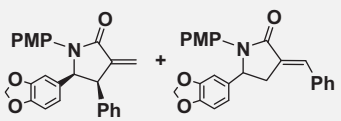
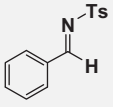
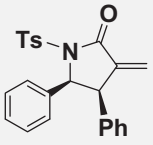
As a conclusion, we demonstrate here an efficient method for the synthesis of *cis*-3,4-diaryl-α-methylene-γ-butyrolactam starting from easily preparable aldimines via sonochemical Barbier-type reaction condition. The 3,4-diaryl-α-methylene-γ-butyrolactams were successfully synthesized by the regioselective allylation of 3-phenylallyl bromide with *N*-tosyl aldimine and only *cis*-stereoisomer was obtained under the reaction condition.



Scheme 1. Allylation reaction of 3-phenalallyl bromide to lime.

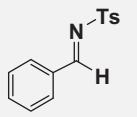
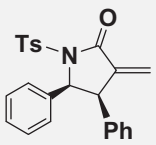
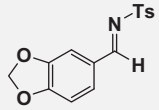
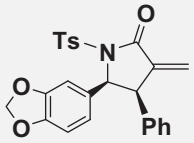
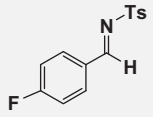
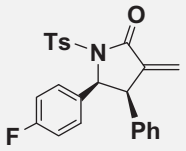
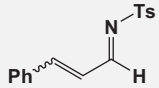
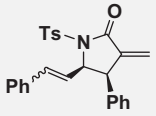
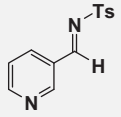
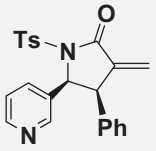
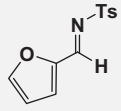
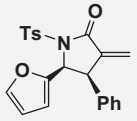
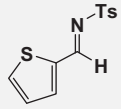
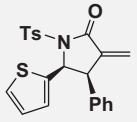
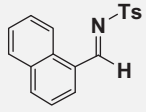
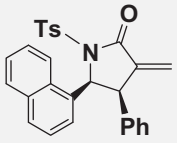
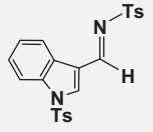
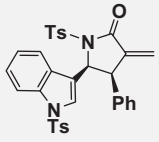
Table 1
Optimization of imine under Barbier-type reaction



Entry	Imine	γ-Lactam	Yield (%)
1			4 + 15
2			35
3			32 + 2
4			72

PMP = *p*-methoxyphenyl, Bn = benzyl, Ts = tosyl.

Table 2
Synthesis of diaryl α-methylene-γ-butyrolactams

Entry	Imine	γ-Lactam	Yield[a] (%)
1			72
2			73
3			63
4			67
5			70
6			81
7			66
8			52
9			41

[a] The yields were determined after chromatography purification.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.057.

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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.