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SHORT COMMUNICATION

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# The Acrylamide Moiety as an Activated Alkene Component in the Intramolecular Baylis–Hillman Reaction: Facile Synthesis of Functionalized α-Methylene Lactam and Spirolactam Frameworks

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**Keywords:** Baylis–Hillman reaction / Lactams / Nitrogen heterocycles / Spiro compounds

A facile strategy for the intramolecular Baylis–Hillman reaction by utilizing an acrylamide moiety as an activated alkene component was developed, which thus provides a convenient protocol for obtaining five- and six-membered α-methylene lactam and spirolactam derivatives.

## Introduction

The Baylis–Hillman (BH) reaction is an emerging continent on the globe of organic chemistry, as it provides diverse classes of proximal densely functionalized molecules possessing high synthetic potential.[1,2] It involves atom-economical construction of carbon–carbon bonds through coupling of activated alkenes with electrophiles under the influence of an appropriate catalyst. The intramolecular BH reaction is a growing branch of BH chemistry that has attracted the attention of synthetic and medicinal chemists, because it produces various carbocyclic and heterocyclic compounds of different ring sizes.[1,3] Although there has been considerable progress in intramolecular BH reactions with the use of various activated alkene components,[3] the application of an acrylamide framework as an activated alkene component has not been well studied.[4] In fact, application of an acrylamide unit as an activated alkene in the regular BH reaction itself has not been studied systematically, possibly due to the lower reactivity of the acrylamide moiety.[5] Therefore, the development of the BH reaction and its intramolecular versions by employing an acrylamide framework as an activated alkene component continues to be a challenging endeavor in BH chemistry.

Although α-methylene (γ- and δ-)lactone skeletons **A**[6] are abundantly available structural organizations in a number of natural products, the presence of α-methylene (γ- and δ-)lactam frameworks **B** are less common among natural products (Figure 1).[7]

However, in recent years α-methylene (γ- and δ-)lactam derivatives have gained increasing importance, as these molecules show various biological activities[8] [cytotoxicity in drug-resistant MDA-MB-231 breast cancer cells,[8a] inhibition activity of homoserine transacetylase (HTA),[8b] and cytotoxicity against leukemia cells].[8c,8d] Therefore, there is increased interest in the development of appropriate synthetic strategies for obtaining these frameworks.[9]

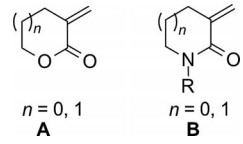
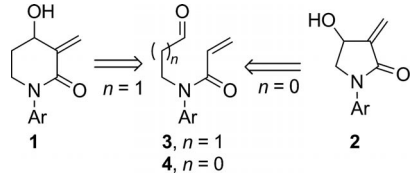



Figure 1. α-Methylene lactone and lactam frameworks.

In continuation of our long-term ongoing research program in this fascinating reaction,[10] we herein report a facile intramolecular BH reaction by using an acrylamide framework as an activated alkene and an aldehyde as the electrophile component. This study provides a useful protocol for obtaining functionalized α-methylene (γ- and δ-)lactam derivatives and also spiropyrrolidin-2-ones in high yields.

## Results and Discussion

We planned the intramolecular BH reaction for obtaining functionalized 3-methylenepiperidin-2-ones **1** and 3-methylenepyrrolidin-2-ones **2** according to the retrosynthetic strategy shown in Scheme 1.




Scheme 1. Retrosynthetic strategy for α-methylene (γ- and δ-)lactam derivatives.

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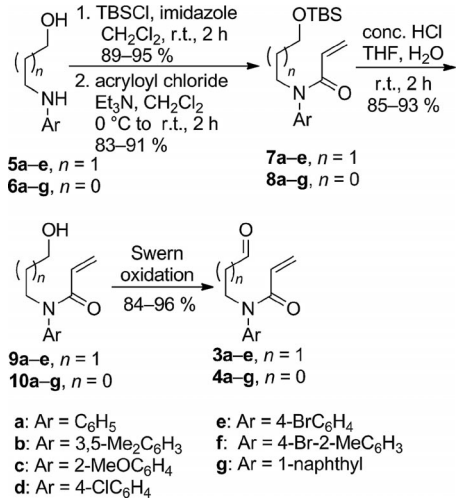
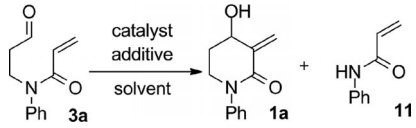
Accordingly, we first selected arylamide–aldehyde (AA) **3a** ($n$ = 1, Ar = phenyl) as a substrate for the intramolecular BH reaction. Required aldehyde **3a** was obtained according to the synthetic sequence shown in Scheme 2 starting from amino alcohol **5a**.[11a] During the initial studies, encouraging yields were obtained if 1,4-diazabicyclo[2.2.2]octane (DABCO, 1.0 equiv.) was used as a promoter and acetonitrile as a solvent at room temperature; these conditions provided desired cyclic allylic alcohol **1a** in 60% yield (Table 1, Entry 1).

To optimize the reaction, we performed it under various conditions [by using different promoters and solvents, by varying the loading of DABCO and selected additives (Table 1)]. The best result was obtained upon treating **3a** (1.0 mM) with DABCO (1.0 mM) in *t*BuOH (6 mL) as the solvent under reflux conditions, which provided desired product **1a** in 75% yield (Table 1, Entry 22). Notably, the formation of substantial amounts of *N*-phenylacrylamide (**11**) was observed (Table 1, Entries 7–15, 19–21, 26–29) under most reaction conditions upon performing the reaction at high temperatures and also in the case of $Bu_3P$ (Table 1, Entries 30 and 31). The formation of acrylamide **11** may be attributed to the abstraction of the proton α to the aldehyde




Scheme 2. Synthesis of acrylamide–aldehydes **3a**–**e** and **4a**–**g**. TBS = *tert*-butyldimethylsilyl.

Table 1. Optimization of the reaction conditions.[a]




| Entry | Solvent | Amount of solvent [mL/mmol of **3a**] | Catalyst (mmol) | Conditions | Additive (5 mol-%) | Time [h] | Yield[b] [%] **1a**[c] | **11**[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 1 | DABCO (1.0) | r.t. | – | 24 | 60 | – |
| 2 | $CH_3CN$ | 1 | DABCO (0.5) | r.t. | – | 60 | 61 | – |
| 3 | $CH_3CN$ | 1 | DABCO (0.25) | r.t. | – | 96 | 58 | – |
| 4 | $CH_3CN$ | 1 | DABCO (2.5) | r.t. | – | 12 | 59 | – |
| 5 | $CH_3CN$ | 3 | DABCO (1.0) | r.t. | – | 60 | 64 | – |
| 6 | $CH_3CN$ | 6 | DABCO (1.0) | r.t. | – | 132 | 71 | – |
| 7 | $CH_3CN$ | 2 | DABCO (1.0) | reflux | – | 6 | 63 | 15 |
| 8 | $CH_3CN$ | 2 | DABCO (1.0) | reflux | $MeSO_3H$ | 6 | 62 | 13 |
| 9 | $CH_3CN$ | 2 | DABCO (1.0) | reflux | TFA | 6 | 65 | 19 |
| 10 | DMF | 2 | DABCO (1.0) | reflux | – | 0.5 | 36 | 47 |
| 11 | DMF | 2 | DABCO (1.0) | reflux | $MeSO_3H$ | 0.5 | 34 | 46 |
| 12 | DMF | 2 | DABCO (1.0) | reflux | TFA | 0.5 | 33 | 48 |
| 13 | *t*BuOH | 2 | DABCO (1.0) | reflux | – | 6 | 66 | 16 |
| 14 | *t*BuOH | 2 | DABCO (1.0) | reflux | $MeSO_3H$ | 6 | 64 | 14 |
| 15 | *t*BuOH | 2 | DABCO (1.0) | reflux | TFA | 6 | 63 | 13 |
| 16 | $CH_3CN$ | 6 | DABCO (1.0) | reflux | – | 36 | 67 | – |
| 17 | $CH_3CN$ | 6 | DABCO (1.0) | reflux | $MeSO_3H$ | 36 | 66 | – |
| 18 | $CH_3CN$ | 6 | DABCO (1.0) | reflux | TFA | 36 | 68 | – |
| 19 | DMF | 6 | DABCO (1.0) | reflux | – | 1 | 31 | 54 |
| 20 | DMF | 6 | DABCO (1.0) | reflux | $MeSO_3H$ | 1 | 35 | 51 |
| 21 | DMF | 6 | DABCO (1.0) | reflux | TFA | 1 | 30 | 55 |
| ***22*** | ***tBuOH*** | ***6*** | ***DABCO (1.0)*** | ***reflux*** | **–** | ***13*** | ***75*** | **–** |
| 23 | *t*BuOH | 6 | DABCO (1.0) | reflux | $MeSO_3H$ | 13 | 72 | – |
| 24 | *t*BuOH | 6 | DABCO (1.0) | reflux | TFA | 13 | 74 | – |
| 25 | DCE | 6 | DABCO (1.0) | reflux | – | 12 | – | – |
| 26 | THF/$H_2O$ (1:1) | 6 | DABCO (1.0) | 65 °C | – | 1.5 | 47 | 15 |
| 27 | $CH_3CN$ | 6 | DMAP (1.0) | reflux | – | 72 | 30 | 34 |
| 28 | DMF | 6 | DMAP (1.0) | reflux | – | 1 | – | 75 |
| 29 | *t*BuOH | 6 | DMAP (1.0) | reflux | – | 72 | 26 | 27 |
| 30 | $CH_3CN$ | 6 | $P(Bu)_3$ (1.0) | r.t. | – | 0.25 | – | 30 |
| 31 | *t*BuOH | 6 | $P(Bu)_3$ (1.0) | r.t. | – | 0.25 | – | 28 |

[a] All reactions were performed on a 1.0 mmol scale of aldehyde **3a**. DCE =1,2-dichloroethane, DMAP = 4-(dimethylamino)pyridine, TFA = trifluoroacetic acid. [b] Yield of isolated, pure product based on the aldehyde. [c] Fully characterized.

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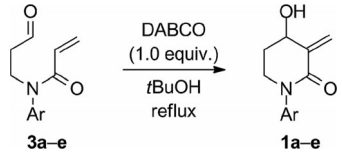
carbonyl group by the base followed by a retro-Michael-type reaction. With the view to understand the generality of this protocol, we prepared representative acrylamide–aldehydes **3b**–**e** by applying the reaction sequence shown in Scheme 2 and subjected them to the intramolecular BH reaction under conditions similar to those used in the case of **3a**. The resulting cyclic allylic alcohols (functionalized 3-methylenepiperidin-2-ones **1b**–**e**) were obtained in 73–78% yield (Table 2).

Table 2. Synthesis of α-methylene δ-lactam derivatives **1a**–**e**.[a]



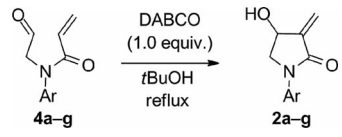

| Entry | AA | Ar | Product[b] | Time [h] | Yield[c] [%] |
|---|---|---|---|---|---|
| 1 | **3a** | $C_6H_5$ | **1a** | 13 | 75 |
| 2 | **3b** | 3,5-$Me_2C_6H_3$ | **1b** | 24 | 77 |
| 3 | **3c** | 2-$MeOC_6H_4$ | **1c** | 84 | 73 |
| 4 | **3d** | 4-$ClC_6H_4$ | **1d** | 6 | 74 |
| 5 | **3e** | 4-$BrC_6H_4$ | **1e** | 6 | 78 |

[a] All reactions were performed on a 1.0 mmol scale of the aldehyde by using DABCO (1.0 equiv.) in *t*BuOH (6.0 mL) at reflux temperature. AA = acrylamide–aldehyde. [b] All products were obtained as white solids and fully characterized (see the Supporting Information). [c] Yield of pure, isolated product based on the aldehyde.

Encouraged by these results, we next focused our attention on the synthesis of five-membered lactam derivatives. Accordingly, we prepared required substrates **4a**–**g** by applying the synthetic sequence described in Scheme 2 starting from amino alcohols **6a**–**g** and subjected them to the BH cyclization reaction (Table 3). We were delighted to see that these reactions were clean and provided corresponding 3-methylenepyrrolidin-2-ones **2a**–**g** in 67–73% yield. The structure of **2d** was further confirmed by single-crystal X-ray diffraction analysis (Figure 2).[12] It is clear from the above results that the BH cyclization of N-aromatic substrates containing electron-donating groups is slower than the cyclization of substrates containing electron-withdrawing groups. This is probably due to the increasing/decreasing electron-donating ability of the nitrogen atom towards the amide carbonyl group. We were pleased to see that the reaction rates for the formation of five-membered lactams **2a**–**g** were faster than those for the formation of six-membered lactams **1a**–**e**.

We also examined a possible asymmetric version of this strategy by using the easily available cinchona alkaloids (amines) quinine and quinidine as reaction promoters in the case of **4a** (Table 3, Entries 8 and 9). These reactions required 30 h for completion, and desired adduct **2a** was obtained in 65 (using quinine) and 63% (using quinidine) yield with low enantioselectivities (10 and 5% *ee*). Though the enantioselectivities were not high, these reactions are encouraging in the sense that there is a possibility to achieve higher enantioselectivities by using appropriate catalysts.

Table 3. Synthesis of α-methylene γ-lactam derivatives **2a**–**g**.[a]




| Entry | AA | Ar | Product[b] | Time [h] | Yield[c] [%] |
|---|---|---|---|---|---|
| 1 | **4a** | $C_6H_5$ | **2a** | 0.5 | 73 |
| 2 | **4b** | 3,5-$Me_2C_6H_3$ | **2b** | 1.5 | 67 |
| 3 | **4c** | 2-$MeOC_6H_4$ | **2c** | 2.5 | 70 |
| 4 | **4d** | 4-$ClC_6H_4$ | **2d**[d] | 0.16 | 71 |
| 5 | **4e** | 4-$BrC_6H_4$ | **2e** | 0.16 | 69 |
| 6 | **4f** | 4-Br-2-$MeC_6H_3$ | **2f** | 1 | 72 |
| 7 | **4g** | 1-naphthyl | **2g** | 1.5 | 70 |
| 8[e] | **4a** | $C_6H_5$ | **2a** | 30 | 65 (10)[f] |
| 9[g] | **4a** | $C_6H_5$ | **2a** | 30 | 63 (5)[f] |

[a] All reactions were performed on a 1.0 mmol scale of the aldehyde by using DABCO (1.0 equiv.) in *t*BuOH (6.0 mL) at reflux temperature. AA = acrylamide–aldehyde. [b] All products were obtained as (colorless/white/yellow/brown) solids and fully characterized (see the Supporting Information). [c] Yield of the pure, isolated product based on the aldehyde. [d] Structure of this compound was also confirmed by single-crystal X-ray diffraction analysis.[12] [e] This reaction was performed on a 1.0 mmol scale of the aldehyde by using quinine (1.0 equiv.). [f] Enantiomeric excess was determined by HPLC analysis by using a chiral column, Chiralcel-OJ-H. [g] This reaction was performed on a 1.0 mmol scale of the aldehyde by using quinidine (1.0 equiv.).

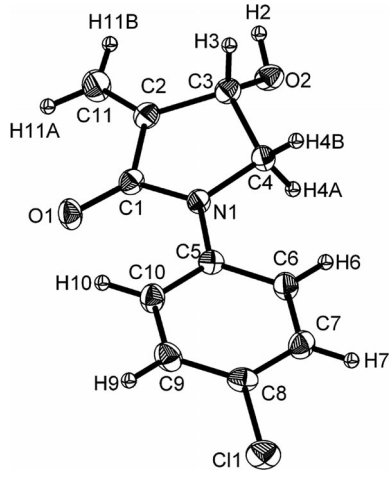



Figure 2. ORTEP diagram (50% probability) of **2d**.

We also performed the intramolecular BH reaction of *N*-(2-oxoethyl)-*N*-phenylcinnamamide (phenyl group at the β-position of the acrylamide). This reaction was not successful even after heating under reflux conditions for 24 h, and most of the starting amide–aldehyde remained intact.

The spiro-γ-lactam framework containing a nitrogen atom α to the spiro center is another important structural skeleton that is an integral part of some interesting natural products[13] and bioactive compounds.[14] Therefore, the development of a facile strategy to obtain such spiro-γ-lactam derivatives has attracted the attention of medicinal and synthetic chemists in recent years.[15]

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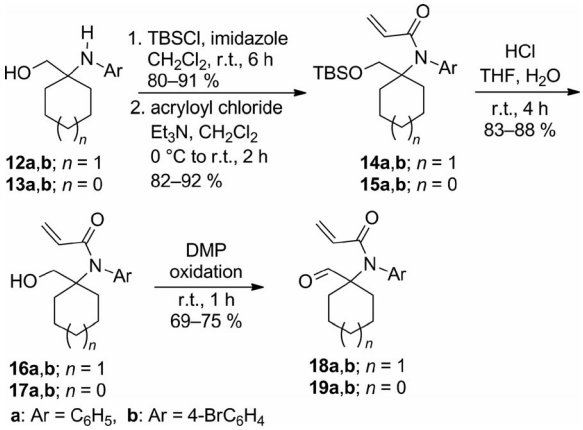
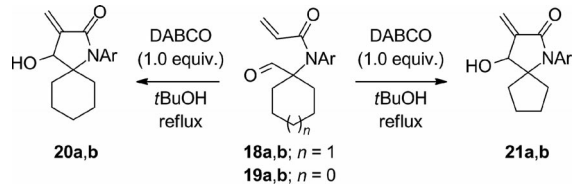



Scheme 3. Synthesis of acrylamide–aldehydes **18a**,**b** and **19a**,**b**. DMP = Dess–Martin periodinane.

Table 4. Synthesis of spiro-γ-lactam derivatives **20a**,**b** and **21a**,**b**.[a]




| Entry | AA | Ar | *n* | Product[b] | Time [h] | Yield[c] [%] |
|---|---|---|---|---|---|---|
| 1 | **18a** | $C_6H_5$ | 1 | **20a**[d] | 10 | 75 |
| 2 | **18b** | 4-$BrC_6H_4$ | 1 | **20b** | 2.5 | 72 |
| 3 | **19a** | $C_6H_5$ | 0 | **21a** | 2 | 68 |
| 4 | **19b** | 4-$BrC_6H_4$ | 0 | **21b** | 0.5 | 70 |

[a] All reactions were performed on a 1.0 mmol scale of the aldehyde by using DABCO (1.0 equiv.) in *t*BuOH (6.0 mL) at reflux temperature. AA = acrylamide–aldehyde. [b] All products were obtained as colorless or white solids and were fully characterized (see the Supporting Information). [c] Yield of the pure, isolated product based on the aldehyde. [d] The structure of this compound was also confirmed by single-crystal X-ray diffraction analysis.[12]

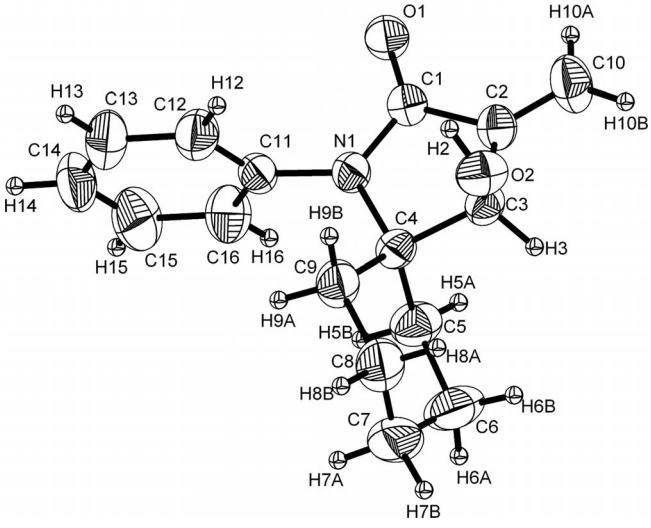



Figure 3. ORTEP diagram (50% probability) of **20a**.

We therefore directed our focus towards the development of an intramolecular BH protocol for the synthesis of these spiro-γ-lactam derivatives containing a nitrogen atom α to the spiro center. Required acrylamide–aldehyde substrates **18a**,**b** and **19a**,**b** were conveniently prepared from amino alcohols **12a**,**b** and **13a**,**b**[11b] according to Scheme 3. Substrates **18a**,**b** and **19a**,**b** were then subjected to the intramolecular BH reaction under conditions similar to those used for **3** and **4** to provide resulting spiro-γ-lactams **20a**,**b** and **21a**,**b** in 68–75% yield (Table 4). The structure of **20a** was further confirmed by single-crystal X-ray diffraction analysis (Figure 3).[12]

## Conclusions

We developed a facile intramolecular BH reaction of substrates containing an acrylamide as an activated alkene (less-explored activated alkene unit) component and an aldehyde as the electrophile component. This protocol provides a convenient strategy for construction of five- and six-membered α-methylene lactam and spirolactam derivatives. This methodology clearly demonstrates the importance of the acrylamide unit as a suitable activated alkene component for intramolecular BH reactions. This strategy also gives opportunities to design new classes of such substrates, which would lead to the construction of various lactam moieties with different ring sizes. Some of our work is in progress in this direction.

## Experimental Section

**Synthesis of 4-Hydroxy-3-methylene-1-phenylpiperidin-2-one (1a) as a Representative Procedure for the Intramolecular Baylis–Hillman Reaction:** A solution of *N*-(3-oxopropyl)-*N*-phenylacrylamide (**3a**; 0.203 g, 1 mmol) and DABCO (0.112 g, 1 mmol) in *t*BuOH (6 mL) was heated under reflux for 13 h (until the disappearance of the aldehyde, as monitored by TLC). The solvent was then removed under reduced pressure, and the crude product thus obtained was purified by column chromatography (silica gel, EtOAc/hexane, 3:1) to furnish title compound **1a** in 75% yield (0.152 g) as a white solid.

**Supporting Information** (see footnote on the first page of this article): General information; experimental procedures; data and copies of the $^1$H and $^{13}$C NMR spectra of compounds **1a**–**e**, **2a**–**g**, **20a**, **20b**, **21a**, and **21b**; ORTEP diagrams of **2d** and **20a**; HPLC traces of racemic **2a** (obtained by using DABCO) and **2a** (with low enantiomeric purity obtained by using quinine and quinidine).

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ities. We are grateful to the National Single-Crystal X-ray Facility funded by the DST. We also thank Prof. S. Pal, School of Chemistry, University of Hyderabad, for helpful discussions regarding single-crystal X-ray diffraction analysis.

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