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Full Research Paper

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Keywords:
[3 + 2] cycloaddition; Heck reaction; hexahydropyrrolo[2,1-a]isoquinoline; one-pot reactions

Abstract
Two kinds of [3 + 2] cycloaddition intermediates generated from the three-component reactions of 2-bromobenzaldehydes and maleimides with amino esters or amino acids were used for a one-pot N-allylation and intramolecular Heck reactions to form pyrrolidinedione-fused hexahydropyrrolo[2,1-a]isoquinolines. The multicomponent reaction was combined with one-pot reactions to make a synthetic method with good pot, atom and step economy. MeCN was used as a preferable green solvent for the reactions.

Introduction
Pyrrolo[2,1-a]isoquinoline and hexahydropyrrolo[2,1-a]isoquinoline are privileged heterocyclic rings existing in many natural products and synthetic compounds possessing antitumor, antibacterial, antiviral, antioxidizing, and other biological activities (Figure 1) [1,2]. For example, the alkaloid crispine A isolated from Carduus crispus L. has antitumor activity [3]. Erythrina alkaloids have curare-like neuromuscular blocking activities [4], and also antioxidant activity against
Multicomponent reactions (MCRs) have been developed as highly efficient tools for assembling heterocyclic scaffolds related to natural products [18-20]. Among the well-established MCRs, three-component 1,3-dipolar cycloadditions of benzaldehydes, maleimides, and amino esters have been developed for making N-containing 5-membered heterocycles (Scheme 1) [21,22]. The [3 + 2] cycloadditions of maleimides with stabilized azomethine ylides I-a generated from the condensation of aldehydes and amino esters for making pyrrolidines II-a have been well-reported [23-26], while the [3 + 2] cycloaddition of the less stable azomethine ylides I-b generated from the reaction of aldehydes and amino acids for pyrrolidines II-b was less explored [27-29].

In recent years, our lab has reported a series of 1,3-dipolar cycloaddition-initiated methods for the synthesis of diverse heterocycles A–J bearing fused polycyclic rings such as tetrahydroepiminobenz[\(b\)]azocines, tetrahydropyrrolobenzodiazepines, triazolobenzodiazepines and tetrahydrochromeno[3,4-b]pyrroline (Scheme 2) [30-39]. Many of these scaffolds were synthesized through the combination of MCR and one-pot synthesis. A literature search indicated that a [3 + 2] cycloaddition-initiated method has also been used for the synthesis of hexahydropyrrolo[2,1-\(a\)]isoquinolines by employing stable 1,3-dilpolar compounds generated from amino
Results and Discussion

Following the reported procedures for amino ester- and amino acid-based [3 + 2] cycloadDITION reactions, pyrrolidine adducts 5 and 6 were synthesized by a three-component reaction of 1 or 2 with 2-bromobenzaldehydes 3 and maleimides 4 (Scheme 3) [30,37]. The cycloaddition reactions were diastereoselective (>20:1 dr for adducts 5 and >6:1 dr for adducts 6). The major diastereomers of 5 and 6 were isolated for following N-allylation and intramolecular Heck reactions.

Scheme 3: [3 + 2] Cycloaddition with amino esters or amino acids. Conditions: 1:3:4 (1:2:1:1.1), Et$_3$N (1.5 equiv), EtOH (3 mL), 110 °C for 6 h; 2:3:4 (1:2:1:1), AcOH (0.3 equiv), MeCN (3 mL), 110 °C for 6 h.
Adduct 5a generated from \([3 + 2]\) cycloaddition was used as a model compound to develop the reaction conditions for the one-pot \(N\)-allylation and intramolecular Heck reactions (Table 1). \(N\)-Allylation of 5a with 3-bromopropene (7) for 8a was accomplished by heating the reaction mixtures in MeCN at 105 °C for 4 h. After evaporating unreacted 3-bromopropene (7) from the reaction mixture, crude product 8a was used for developing the intramolecular Heck reaction by screening Pd(II) catalysts, ligands, bases, additives, solvents, temperatures and reaction time (Table 1). The initial intramolecular Heck reactions were carried out using 10 mol % of Pd(OAc)\(_2\) or 10 mol % of PdCl\(_2\) with 20 mol % of PPh\(_3\) as a ligand and 2 equiv of K\(_2\)CO\(_3\) in MeCN at 80 °C for 10 h without additive to give 6-\(exo\)-cyclized product 9a in 32% and 18% yields, respectively (Table 1, entries 1 and 2). Addition of NaOAc increased the yield of 9a to 71% (Table 1, entry 3). Other attempts to improve the Heck reaction using different ligands, such as (P(o-tol))\(_3\), PCy\(_3\) and dpdm, were not successful (Table 1, entries 4–6). The reaction at 105 °C in MeCN gave 9a in 78% yield (Table 1, entry 7), while at 120 °C in DMF gave 9a in 77% yield (Table 1, entry 11). Reducing the amount of Pd(OAc)\(_2\) to 5 mol % or the reaction temperature to 40 °C gave lower product yields (Table 1, entries 8 and 10). Double the amount of Pd(OAc)\(_2\) to 20 mol % gave 9a in 79% yield, just 1% increase than that of using 10 mol % of catalyst (Table 1, entry 9). Besides K\(_2\)CO\(_3\), other bases including Na\(_2\)CO\(_3\), Cs\(_2\)CO\(_3\) and Et\(_3\)N were also used for the Heck reaction, but none of them improved the product yield (Table 1, entries 12–14). A base-free control reaction gave 9a in 10% yield (Table 1, entry 15). Thus, the optimized conditions for the Heck reaction was to use 10 mol % of Pd(OAc)\(_2\), 20 mol % of PPh\(_3\), 2 equiv of K\(_2\)CO\(_3\) and 1 equiv of NaOAc in 3 mL of MeCN at 105 °C for 3 h which give 9a in 78% yield (Table 1, entry 7). It is worth noting that there was no 9ab observed as a byproduct because 6-\(exo\) cyclization is more favorable [50,51].

The optimized reaction conditions were then employed for the synthesis of analogs of 9 (Scheme 4). A variety of \([3 + 2]\) cycloaddition adducts 5 bearing different R, R\(^1\), R\(^2\) and R\(^3\) groups, derived from amino esters 1, 2-bromobenzaldehydes 3 and maleimides 4, were subjected to \(N\)-allylation followed by intramolecular Heck reaction to pyrrolidinedione-fused hexahy-

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**Table 1: Optimization of the one-pot reaction conditions.**

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<th>base</th>
<th>additive</th>
<th>solvent</th>
<th>temp [°C]</th>
<th>time [h]</th>
<th>yield [%]</th>
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\(^{a}\)Reaction conditions: 0.5 mmol 5a in 3 mL MeCN, 7 (3 equiv), K\(_2\)CO\(_3\) (2 equiv) for \(N\)-allylation; Pd catalyst (10 mol %), ligand (20 mol %), base (2 equiv) and NaOAc (1 equiv) in 3 mL solvent under nitrogen for the Heck reaction; P(o-tol)\(_3\) = tri(o-tolyl)phosphine, dpdm = 1,1-bis(diphenylphosphino)methane. \(^{b}\)Isolated yield. \(^{c}\)Pd(OAc)\(_2\) 5 mol %, PPh\(_3\) 10 mol %, \(^{d}\)Pd(OAc)\(_2\) 20 mol %, PPh\(_3\) 40 mol %.
Scheme 4: Synthesis of pyrrolo[2,1-α]isoquinolines 9. Reaction conditions: 5 (0.5 mmol, 1 equiv), 7 (3 equiv) and K₂CO₃ (2 equiv) in MeCN (3 mL) for N-allylation; then Pd(OAc)₂ (10 mol %), PPh₃ (20 mol %), K₂CO₃ (2 equiv) and NaOAc (1 equiv) in MeCN (3 mL) under nitrogen for the Heck reaction. Isolated yield.

We next employed intermediated 6 prepared from the decarboxylative [3+2] cycloaddition of amino acids for one-pot N-allylation and intramolecular Heck reactions under the same optimized conditions developed in Table 1. Pyrrolidinedione-fused hexahydropyrrolo[2,1-α]isoquinoline 11a–i were produced in 65–78% yields also as single isomers (Scheme 5).

Allylation of [3 + 2] adducts 5 or 6 with cinnamyl bromide were also conducted and the intermediates were used for the Heck reaction for making products 12a–d (Scheme 6). Even the allylated intermediates were not terminal alkenes, the Heck reaction gave the Z-products exclusively [52].

A general mechanism for Pd-catalyzed intramolecular Heck reaction of 8a for the synthesis of pyrrolo[2,1-α]isoquinoline 9a is shown in Scheme 7. The oxidative addition of the Pd(0) species to alkene intermediate 8a leads to Pd-complex 1. Intramo...
Scheme 5: Synthesis of pyrrolo[2,1-a]isoquinolines 11. Reaction conditions: 6 (0.5 mmol, 1 equiv), 7 (3 equiv) and K$_2$CO$_3$ (2 equiv) in MeCN (3 mL) for the N-allylation; then Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), K$_2$CO$_3$ (2 equiv) and NaOAc (1 equiv) in MeCN (3 mL) under nitrogen for the Heck reaction. Isolated yield.

Scheme 6: Synthesis of pyrrolo[2,1-a]isoquinolines 12. Reaction conditions: 5 or 6 (0.5 mmol, 1 equiv), cinnamyl bromide (3 equiv) and K$_2$CO$_3$ (2 equiv) in MeCN (3 mL) for the N-allylation; then Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), K$_2$CO$_3$ (2 equiv) and NaOAc (1 equiv) in MeCN (3 mL) under nitrogen for the Heck reaction. Isolated yield.

Molecular coordination of Pd-complex I with the C–C double bond forms complex II which is followed by the syn insertion of alkene to give complex III [50,51]. Subsequent β-hydride elimination of III gives complex IV which undergoes dissociation to afford product 9a. The hydridopalladium(II) halide is converted to the catalytically active Pd(0) with a base.
Conclusion

In summary, we have developed an efficient method through a three-component [3 + 2] cycloaddition followed by a one-pot \( N \)-allylation and an intramolecular Heck reaction for the synthesis of pyrrolinedione-fused hexahydropyrrolo[2,1-\( a \)]isoquinolines. Two different kinds of [3 + 2] adducts generated from the reactions of amino esters or amino acids were used as the key intermediates for sequential transformations. A high synthetic efficiency was achieved by the combination of a three-component reaction with one-pot reactions. This synthetic sequence is a new addition of our [3 + 2] cycloaddition-initiated reactions for making diverse cyclic scaffolds.

General procedure for the synthesis of pyrrolidine adducts 6

A solution of 2-aminoisobutyric acid (2, 1.2 mmol), 2-bromobenzaldehyde (3, 1 mmol) and maleimide (4, 1 mmol) in MeCN (3 mL) with AcOH (0.3 mmol) was heated at 110 °C for 6 h in a sealed vial. The concentrated reaction mixture was isolated by column chromatography on silica gel to afford adduct 6 in 75–85% yield.

General procedure for the synthesis of pyrrolo[2,1-\( a \)]isoquinolines 9 or 11

To a solution of pyrrolidine adduct 5 or 6 (0.5 mmol), 3-bromopropene (7, 1.5 mmol) in MeCN (3 mL) was added \( \text{K}_2\text{CO}_3 \) (1 mmol), the mixture was heated at 105 °C for 4 h in a sealed vial. Upon the completion of reaction as monitored by HPLC or LC–MS, the mixture was evaporated under vacuum to remove unreacted 3-bromopropene to give crude \( N \)-allylation intermediate 8 or 10. Without further purification, it was used for the Heck reaction with Pd(OAc)\(_2\) (0.05 mmol), PPh\(_3\) (0.1 mmol), \( \text{K}_2\text{CO}_3 \) (1 mmol) and NaOAc (0.5 mmol) in MeCN (3 mL) at 105 °C for 3 h under nitrogen atmosphere. After aqueous work up, the crude product was purified by flash chromatography to afford product 9 or 11.
General procedure for the synthesis of pyrrolo[2,1-a]isoquinolines 12
To a solution of pyrrolidine adduct 5 or 6 (0.5 mmol), cinnamyl bromide (1.5 mmol) in MeCN (3 mL) was added K₂CO₃ (1 mmol), the mixture was heated at 105 °C for 4 h in a sealed vial. Upon the completion of reaction as monitored by HPLC or LC–MS, the mixture was evaporated and the unreacted cinnamyl bromide was isolated to give N-allylation intermediate which was then used for the Heck reaction with Pd(OAc)₂ (10 mol %), PPh₃ (2 equiv) and NaOAc (1 equiv) in MeCN (3 mL) at 105 °C for 3 h under nitrogen atmosphere. After aqueous work-up, the crude product was purified by flash chromatography to afford product 12.

Supporting Information
Supporting Information File 1
General reaction procedures, compound characterization data, and copies of NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-106-S1.pdf]

Acknowledgements
We thank Prof. Jian Li for the discussion of this paper. We also thank Huimin Zhang’s early work for this project.

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Preprint
A non-peer-reviewed version of this article has been previously published as a preprint doi:10.3762/bxiv.2020.28.v1

References