Preprint Title	Synthesis of pyrrolidinedione-fused hexahydropyrrolo[2,1-*a*]isoquinolines *via* three-component [3+2] cycloaddition followed by one-pot *N*-allylation and intramolecular Heck reactions
Authors	Xiaoming Ma, Suzhi Meng, Xiaofeng Zhang, Qiang Zhang, Shenghu Yan, Yue Zhang and Wei Zhang
Publication Date	16 Mär 2020
Article Type	Full Research Paper
Supporting Information File 1	20-3-15 SupInf.pdf; 6.1 MB
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Synthesis of pyrrolidinedione-fused hexahydropyrrolo[2,1-*a*]isoquinolines *via* three-component [3+2] cycloaddition followed by one-pot *N*-allylation and intramolecular Heck reactions

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

Abstract

Two kinds of [3+2] cycloadditions intermediates generated from the three-component reactions of 2-bromobenzaldehydes and maleimides with amino esters or amino acids were used for 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 the 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*]isoquinolines are privileged heterocyclic rings existed in many nature products and synthetic compounds possessing antitumor, antibacterial, antiviral, antioxidizing, and other biological activities (Figure 1) [1,2]. For examples, 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 DPPH free radical

[5]. Lamellarins isolated from marine invertebrates [6] are inhibitors for HIV-1 integrase and also have immuno modulatory activity [7,8]. Trolline has inhibitory activity for Gram-negative and -positive bacteria [9], also as free radical scavenger in rat brain [10]. Organic chemists have contentiously interested in the development of methods for the synthesis of pyrrolo[2,1-*a*]isoquinolines and related ring systems [11-15], while medicinal chemists have also interested in making related compounds for biological screening and drug development [16,17].

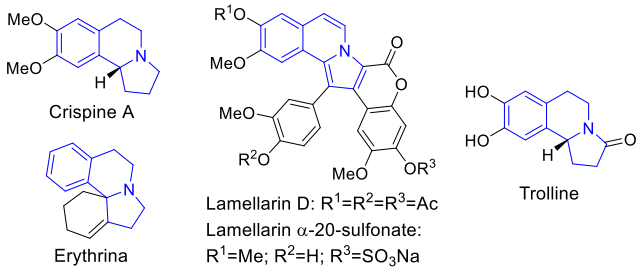
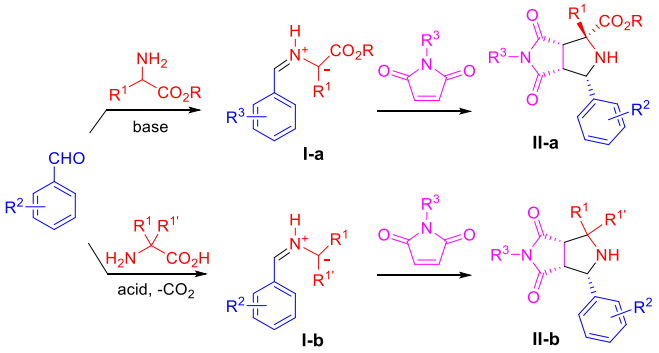


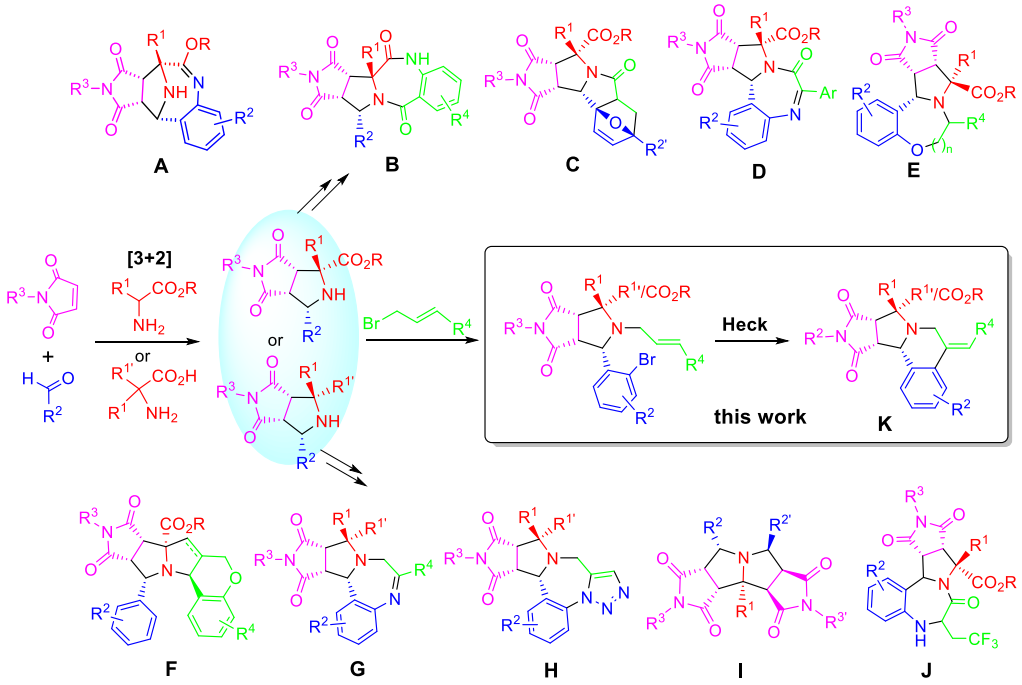
Figure 1: Bioactive pyrrolo[2,1-*a*]isoquinolines and hexahydropyrrolo[2,1-*a*]isoquinolines

Multicomponent reactions (MCRs) have been developed as a highly efficient tool 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 [3+2] of less stable azomethine ylides **I-b** generated from the reaction of aldehydes and amino acids for pyrrolidines **II-b** was less explored [27-29].



Scheme 1: [3+2] Cycloaddition with amino esters or amino acids

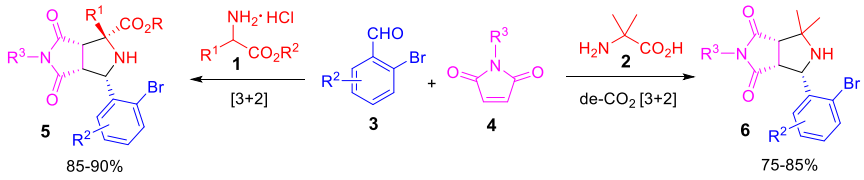
In recent years, our lab has reported a series of 1,3-dipolar cycloaddition-initiated methods for the synthesis of diverse heterocycles **A**-**J** bearing fused polycyclic rings such as tetrahydroepimino-benzo[*b*]azocines, tetrahydro-pyrrolobenzodiazepinones, triazolobenzodiazepines and tetrahydro-chromeno[3,4-*b*]pyrrolizine (Scheme 2) [30-39]. Many of these scaffolds were synthesized through the combination of MCR and one-pot synthesis. Literature search indicated that [3+2] cycloaddition-initiated method has also been used for the synthesis of hexahydropyrrolo[2,1-*a*]isoquinolines by employing stable 1,3-dilpolars generated from amino esters [15,40] or isoquinolines [41-49]. We like to report in this paper our effort on the synthesis of pyrrolidinedione-fused hexahydropyrrolo[2,1-*a*]isoquinolines *via* sequential 1,3-dipolar cycloaddition, *N*-allylation, and intramolecular Heck cyclization reactions (Scheme 2, **K**). Both stabilized and non-stable azomethine ylides could be used for the initial [3+2] cycloaddition reactions. A multicomponent reaction was combined with one-pot reactions to make it a green synthetic method with pot, atom and step economy (PASE) [50,51].



Scheme 2: Scaffolds derived from the initial [3+2] adducts

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 3-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.

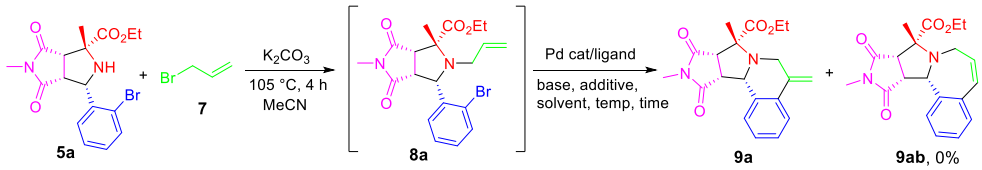


Conditions: **1:3:4** (1.2:1:1.1), Et_3N (1.5 equiv), EtOH (3 mL), 110 °C for 6 h; **2:3:4** (1.2:1:1), AcOH (0.3 equiv), MeCN (3 mL), 110 °C for 6 h.

Scheme 3: [3+2] Cycloaddition with amino esters or amino acids

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 for **8a** was accomplished by heating the reaction mixtures in MeCN at 105 °C for 4 h. After evaporating unreacted 3-bromopropene 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

Table 1: Optimization of the one-pot reaction conditions[a]



Entry	Pd Cat.	Ligand	Base	Additive	Solvent	Temp/°C	Time/h	Yield/%[d]
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	-	MeCN	80	10	32
2	$PdCl_2$	PPh_3	K_2CO_3	-	MeCN	80	10	18
3	$Pd(OAc)_2$	PPh_3	K_2CO_3	NaOAc	MeCN	80	6	71
4	$Pd(OAc)_2$	P(*o*-tol)$_3$	K_2CO_3	NaOAc	MeCN	80	6	61
5	$Pd(OAc)_2$	PCy_3	K_2CO_3	NaOAc	MeCN	80	6	45
6	$Pd(OAc)_2$	dppm	K_2CO_3	NaOAc	MeCN	80	6	58
7	**$Pd(OAc)_2$**	**PPh_3**	**K_2CO_3**	**NaOAc**	**MeCN**	**105**	**3**	**78**
8[b]	$Pd(OAc)_2$	PPh_3	K_2CO_3	NaOAc	MeCN	105	3	28
9[c]	$Pd(OAc)_2$	PPh_3	K_2CO_3	NaOAc	MeCN	105	3	79
10	$Pd(OAc)_2$	PPh_3	K_2CO_3	NaOAc	MeCN	40	12	13
11	$Pd(OAc)_2$	PPh_3	K_2CO_3	NaOAc	DMF	120	3	77
12	$Pd(OAc)_2$	PPh_3	Na_2CO_3	NaOAc	MeCN	105	6	19
13	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	NaOAc	MeCN	105	6	34
14	$Pd(OAc)_2$	PPh_3	Et_3N	NaOAc	MeCN	105	6	11
15	$Pd(OAc)_2$	PPh_3	-	NaOAc	MeCN	105	6	10

[a] Reaction conditions: 0.5 mmol **5a** in 3 mL MeCN, **7** (3 equiv), K_2CO_3 (2 equiv) for *N*-allylation; Pd catalyst (10 mol%), ligand (20 mol%), base (2 euqiv) and NaOAc (1 equiv) in 3 mL solvent under nitrogen for the Heck reaction; P(*o*-tol)$_3$ = tri(*o*-tolyl)phosphine, dppm = 1,1-bis(diphenylphosphino) methane. [b] $Pd(OAc)_2$ 5 mol%, PPh_3 10 mol%. [c] $Pd(OAc)_2$ 20 mol%, PPh_3 40 mol%.
[d] Isolated yield.

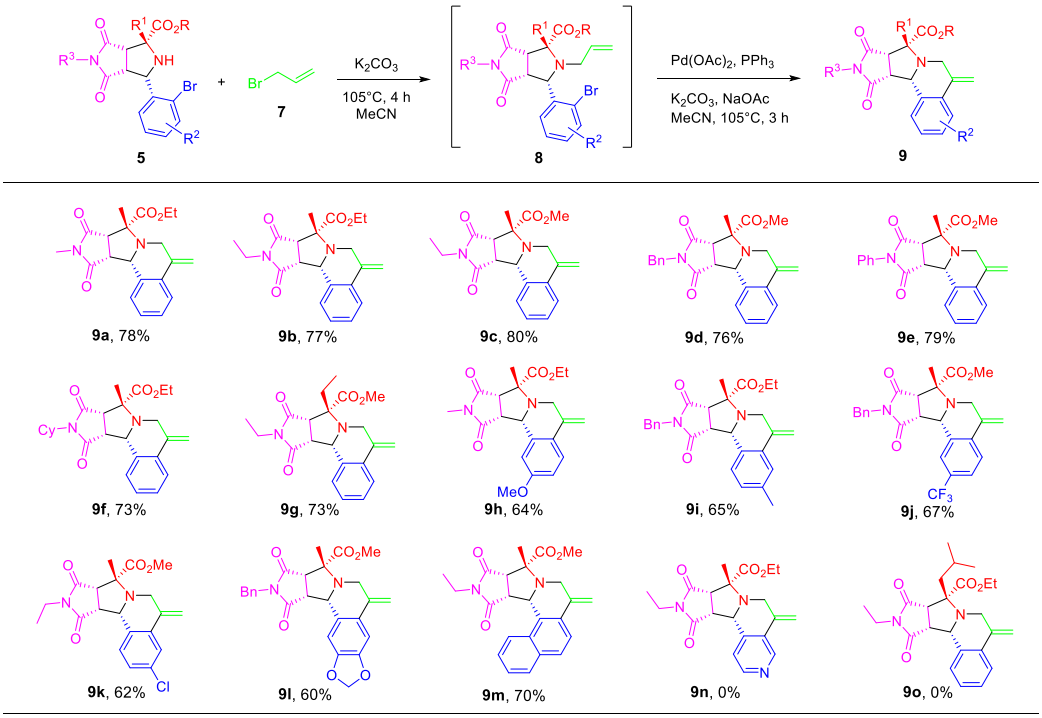
as a ligand and 2 equiv of K_2CO_3 in MeCN at 80 °C for 10 h without additive to give *6-exo* cyclized product **9a** in 32% and 18% yields, respectively (Table 1, entries 1 & 2). Addition of NaOAc increased the yield of **9a** to 71% (Table 1, entry 3). Other attempts to improve the Heck reaction using different ligands, such as (P(*o*-tol)$_3$, PCy_3 and dppm, 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 reaction temperature to 40 °C gave lower product yields (Table 1, entries 8 & 10). Double the amount $Pd(OAc)_2$ 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_2CO_3, other bases including Na_2CO_3, Cs_2CO_3 and Et_3N 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 condition for the Heck reaction was to use 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3, 2 equiv of K_2CO_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** was observed as a byproduct because *6-exo* cyclization is more favorable [52,53].

The optimized reaction conditions were then employed for the synthesis of analogs of **9a** (Table 2). 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 hexahydropyrrolo[2,1-*a*]isoquinoline compounds **9a**-**o** in moderate to good yields as a single isomers which were confirmed by ^{1}H NMR analysis of the crude reaction mixtures. The substitution groups R^3 (Me, Et, Ph, Bn, *c*-C_6H_{11}) on maleimide have no significant influence on the product yields to afford **9a**-**f** in 73-80% yields. The substituent groups R^2 including donation (Me, OMe, -OCH_2O) or withdrawing groups (CF_3, Cl) on the benzene ring have a little effect on the yield of products **9h-l**. Product **9m** bearing a naphthyl group was produced in 70% yield. Product **9n** containing a pyridine ring was not obtained due to the low yield at the *N*-allylation step. Same result happened to **9o** in which hindered *i*-Bu blocked the *N*-allylation.

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-*a*]isoquinoline **11a-i** were

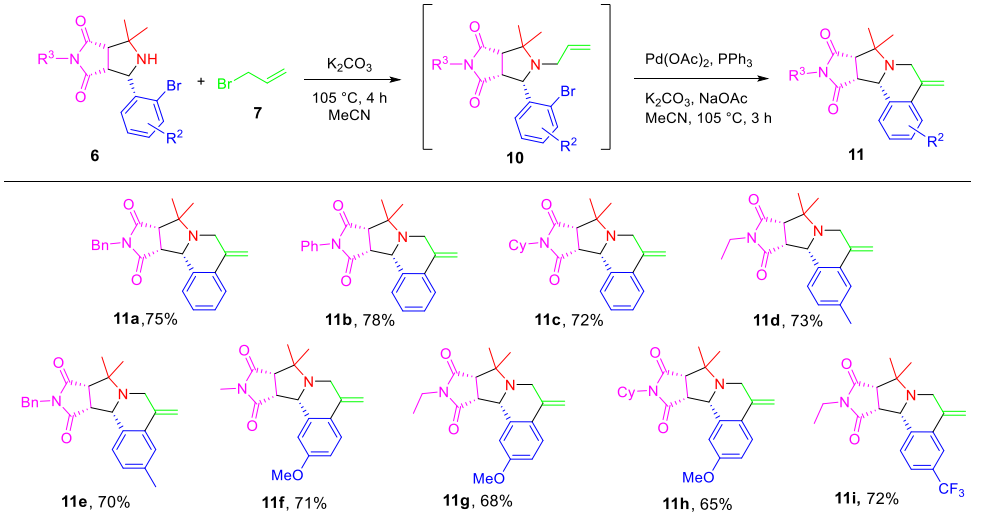
produced in 65-78% yields also as single isomers (Table 3).

Table 2. Synthesis of pyrrolo[2,1-*a*]isoquinolines **9**[a]



[a] Conditions: **5** (0.5 mmol, 1 equiv), **7** (3 equiv) and K_2CO_3 (2 equiv) in MeCN (3 mL) for *N*-allylation; then $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 euqiv) and NaOAc (1 equiv) in MeCN (3 mL) under nitrogen for the Heck reaction. Isolated yield.

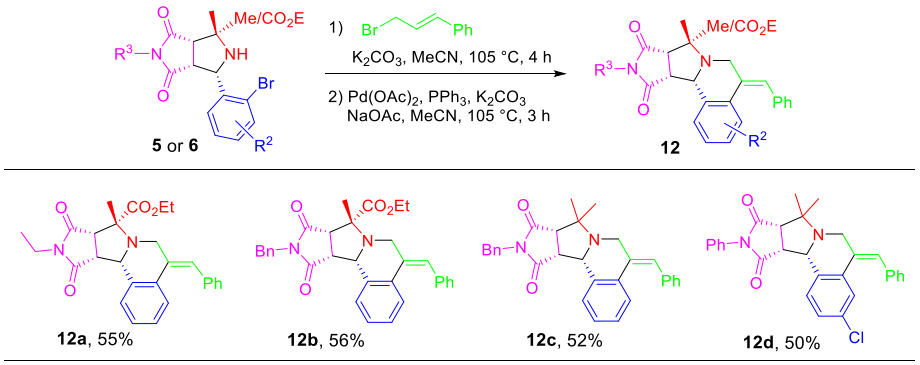
Table 3: Synthesis of pyrrolo[2,1-*a*]isoquinolines **11**[a]



[a] Conditions: **6** (0.5 mmol, 1 equiv), **7** (3 equiv) and K_2CO_3 (2 equiv) in MeCN (3 mL) for *N*-allylation; then $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 euqiv) and NaOAc (1 equiv) in MeCN (3 mL) under nitrogen for the Heck reaction. Isolated yield.

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**. Even the allylated intermediates were not terminal alkenes, the Heck reaction gave the *Z*-products exclusively [54].

Table 4: Synthesis of pyrrolo[2,1-*a*]isoquinolines **12**[a]



[a] Conditions: **5** or **6** (0.5 mmol, 1 equiv), cinnamyl bromide (3 equiv) and K_2CO_3 (2 equiv) in MeCN (3 mL) for *N*-allylation; then $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), K_2CO_3 (2 equiv) and NaOAc (1 equiv) in MeCN (3 mL) under nitrogen for the Heck reaction. Isolated yield.

Conclusion

In summary, we have developed an efficient method through three-component [3+2] cycloaddition followed by one-pot *N*-allylation and intramolecular Heck reaction for tshe synthesis of pyrrolidinedione-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. 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.

Experimental

General procedures for the synthesis of pyrrolidine adducts **5**

A solution of amino ester **1** (1.2 mmol), 2-bromobenzaldehyde **3** (1 mmol) and maleimide **4** (1.1 mmol) in EtOH (3 mL) with Et_3N (1.5 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 **5** in 85-90% yield.

General procedures 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 procedures 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 K_2CO_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), K_2CO_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 procedures 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 K_2CO_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 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%), PPh_3 (20 mol%), K_2CO_3 (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.

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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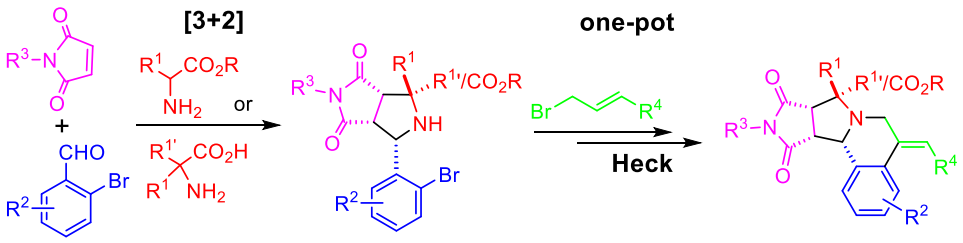
Graphical Abstract



PASE synthesis, MeCN as a preferable green solvent