Preprint Title: One-pot Ugi-azide and Heck reactions for the synthesis of heterocyclic systems containing tetrazole and 1,2,3,4-tetrahydroisoquinoline

Authors: Jiawei Niu, Yuhui Wang, Shenghu Yan, Yue Zhang, Xiaoming Ma, Qiang Zhang and Wei Zhang

Publication Date: 18 Jan. 2024

Article Type: Full Research Paper

Supporting Information File 1: 24-1-16 SupInf.pdf; 3.2 MB

ORCID® iDs: Xiaoming Ma - https://orcid.org/0000-0003-1358-428X; Wei Zhang - https://orcid.org/0000-0002-6097-2763
One-pot Ugi-azide and Heck reactions for the synthesis of heterocyclic systems containing tetrazole and 1,2,3,4-tetrahydroisoquinoline

Jiawei Niu1‡, Yuhui Wang1‡, Shenghu Yan1, Yue Zhang1, Xiaoming Ma*1, Qiang Zhang*2, Wei Zhang*3

Addresses: 1 School of Pharmacy, Changzhou University, 1 Gehu Road, Changzhou 213164, China 2 School of Chemistry and Life Sciences, Suzhou University of Science and Technology, 99 Xuefu Road, Suzhou 215009, China 3 Department of Chemistry and Center for Green Chemistry, University of Massachusetts Boston, 100 Morrissey Blvd, Boston, MA 02125, USA

Email: Xiaoming Ma’ - mxm.wuxi@cczu.edu.cn, Qiang Zhang’ - qzhang@mail.usts.edu.cn, Wei Zhang’ - wei2.zhang@umb.edu

‡These authors contributed equally to this work
*Corresponding authors

Keywords: Ugi-azide reaction; Heck reaction; one-pot; tetrazole; tetrahydroisoquinoline; tetrazolo-pyrazino[2,1-a]isoquinolin-6(5H)-ones

Abstract

A new method for the synthesis of heterocyclic systems containing tetrazole and tetrahydroisoquinoline is developed via the performance of one-pot Ugi-azide and Heck cyclization reactions. The integration of the multicomponent and post-condensation reactions in one-pot maximizes the pot-, atom-, and step-economy (PASE).

Introduction

Tetrazole is a privileged heterocycle existing in a range of biological and medicinally interested compounds [1,2] with antifungal [3,4], antibacterial [5], anticancer [6,7], anti-parasitic [8], antihypertensive properties [9] including the FDA approved drugs such as valsartan and cefmetazole [10,11] (Figure 1). The tetrazole ring can also be found in functional materials for photography, imaging, and military applications [12–17]. The hydroisoquinoline core, such as 1,2,3,4-tetrahydroisoquinoline and pyrazino[2,1-a]isoquinolinone, is also a privileged heterocycle which can be found in natural products and synthetic compounds with anti-tumor, anti-HIV, anti-biotic, antifungal, anti-virus, and anti-inflammatory activities [18–21]. The antischistosomal drug
praziquantel (PZQ), a tetrahydroisoquinoline derivative, is a commercialized drug for the treatment of schistosomiasis [22–25]. The combination of privileged heterocycles of tetrazole and tetrahydroisoquinoline generates new molecules which could have biological activities.

A standard Ugi four-component reaction (Ugi-4CR) of aldehyde, amine, isocyanide, and carboxylic acid produces a peptidic structures A with up to four points of substitution diversity (Scheme 1) [26,27]. By replacing the carboxylic acid with a nucleophilic azide reagent $XN_3$ (generally TMSN$_3$), the Ugi-azide four-component reaction (UA-4CR) of aldehyde, amine, isocyanide, and azide gives 1,5-disubstituted $1H$-tetrazoles (1,5-DS-$1H$-Ts) B. The performance of post-condensation reaction of UA-4CR adducts has resulted various 1,5-DS-$1H$-Ts containing heterocyclic compounds [28–32], such as bis-heterocyclic lactam-tetrazoles [33,34], 2-tetrazolylmethyl-2,3,4,9-tetrahydro-$1H$-$\beta$-carbolines [35], ketopiperazines-tetrazoles [36], imidazo-tetrazolodiazepinones [37], tetracyclic tetrazolyl pyridoimidazo quinolines [38], bis-heterocyclic 1,5-disubstituted tetrazole-indolizine [39] and ($E$)-12-tetrazolyl-5$H$-quinazolinol[3,2-$a$]quinazolines [40]. Among them, the Hulme group reported a UA-4CR/post-condensation sequence to give fused imidazo-tetrazolodiazepinones (Scheme 2, A) [37]. The Gámez-Montaño group introduced a one-pot synthesis of Ugi-azide/N-acylation/Diels-Alder/dehydration reactions for isoindolin-1-one and 1,5-DS-T in a linked manner (Scheme 2, B) [41]. The Ding group developed sequential Ugi-azide/Ag-catalyzed oxidative cycloisomerization reactions for the synthesis of 2-tetrazolyl-substituted 3-acylpyrroles (Scheme 2, C) [42]. The Ding group also reported sequential Ugi-azide/Staudinger/aza-Wittig/addition/Ag-catalyzed cyclization reactions for making 12-tetrazolyl substituted ($E$)-$5H$-quinazolinol[3,2-$a$]quinazolines (Scheme 2, D) [40].

![Figure 1: Representative bioactive tetrazole- and tetrahydroisoquinoline-containing compounds.](image-url)
Scheme 1: The Ugi and Ugi-azide reactions.

A) Hulme’s work: Sequential Ugi-azide/ring-closure (ref 37)

B) Gamez-Montano’s work: One-Pot Ugi-azide/N-acylation/Diels-Alder/dehydration (ref 41)

C) Ding’s work: Sequential Ugi-Azide/Ag-catalyzed oxidative cycloisomerization (ref 42)

D) Ding’s work: Sequential Ugi-azide/Staudinger/aza-Wittig/addition/Cyclization (ref 40)

Scheme 2: Ugi-azide and post-condensations for various heterocyclic scaffolds.

There are numbers of Ugi and subsequential Heck (or reductive Heck) reactions that have been developed for the synthesis of poly-heterocyclic compounds [43–51]. Reported in this paper is a one-pot Ugi-azide followed by the intramolecular Heck reactions for the synthesis of tetrazolyl-1,2,3,4-tetrahydroisoquinoline scaffolds 6 and 8 (Scheme 3). The first step is the Ugi-azide reaction of 2-bromobenzoaldehyde 1, allylamine hydrochloride 2, azidotrimethylsilane (TMSN₃) 3 and isocyanide 4 for tetrazoles 5. If the ethyl isocyanoacetate is used as the isocyanide source, the Ugi-azide reaction could afford ring-fused tetrazolo[1,5-a]pyrazin-6(5H)-one adducts 5. The Pd-catalyzed intramolecular Heck reaction of 5 or 7 afford 1,2,3,4-tetrahydroisoquinolines 6 and 8, respectively.
Results and Discussion

Following the reported procedures [41], the Ugi-azide reaction of 2-bromobenzaldehyde 1a (1 mmol), allylamine hydrochloride 2 (1 mmol), trimethylsilyl azide 3 (1 mmol) and tert-butyl isocyanide 4a (1 mmol) in MeOH at 40 °C for 24 h afforded 1,5-DS-1H-T 5a in 92% yield after chromatography purification. Our effort was then focused on the optimization of the intramolecular Heck reaction of 5a for making 1,2,3,4-tetrahydroisoquinoline 6a. A systematic evaluation of different catalysts and ligands, solvents, bases, as well as reaction temperatures and time was conducted (Table 1). The Heck reaction of 5a was first examined by using 10 mol % Pd(OAc)$_2$, 20 mol % PPh$_3$, 2 equiv of Et$_3$N in CH$_3$CN or DMF at 105 °C for 24 h under N$_2$ atmosphere. But the reactions were failed under the conditions (Table 1, entries 1 and 2). When K$_2$CO$_3$ was used as a base to replace Et$_3$N, the reactions in either CH$_3$CN or DMF for 3 h both gave cyclized product 6a in 70% yield (entries 3 and 4). The increase of the reaction time to 12 h didn’t improve the yield (entry 5). The reaction was further evaluated in the absence of ligand which afforded the product in 35% yield (entry 6). Screening of ligands, e.g. PCy$_3$ and P(o-tol)$_3$ reduced the yield of 6a (entries 7 and 8). Lowering the amount of Pd(OAc)$_2$ or changing the reaction temperatures resulted low yields of 6a (entries 9-11). Similar results were observed from the reactions using other bases, such as K$_3$PO$_4$, NaOAc and Cs$_2$CO$_3$ (entries 12-14). Investigation of other Pd catalysts PdCl$_2$ and Pd(dba)$_2$ also gave low yields (entries 15 and 16). Since CH$_3$CN is a more favorable than DMF in green chemistry consideration [52,53], the optimal reaction conditions for the Heck reaction is to use 1 mmol of 5a with 10 mol% Pd(OAc)$_2$ and 20 mol% PPh$_3$, 2 equiv of K$_2$CO$_3$ in 3 mL CH$_3$CN at 105 °C for 3 h under N$_2$ atmosphere which affords 6a in 70% yield (entry 3).
The combination of an initial multicomponent reaction with post-condensation reactions in one-pot is a good strategy to develop high pot, atom and step economy (PASE) synthesis [54–58]. We then made the effort to integrate the Ugi and Heck reactions in one-pot for making tetrazolyl-1,2,3,4-tetrahydroisoquinolines 6. Thus, a mixture of 2-bromobenzaldehyde 1a (1 mmol), allylamine hydrochloride 2 (1 mmol), trimethylsilyl azide 3 (1 mmol) and tert-butyl isocyanide 4a (1 mmol) was stirred in MeOH at 40 °C for 24 h, after the reaction was completed, the solvent was evaporated under vacuum to give crude Ugi adduct 5a which was used for the intramolecular Heck reaction without further purification. Thus, the crude 5a in MeCN (3 mL) was used for the Heck reaction with 10 mol% of Pd(OAc)2, 20 mol% of PPh3, 2 equiv of K2CO3 for 3 h at 105 °C under N2 atmosphere to give 6a in 60% isolated yield (entry 17).

With the optimized one-pot reactions in hands, we evaluated the substrate scope by making 11 derivatives (Scheme 5) using nine benzaldehydes 1, two isonitriles or ethyl isocyanooacetate 4, allylamine hydrochloride 2, and trimethylsilyl azide 3 for the initial Ugi-azide. Among them, products 6a–b from the reaction of isonitriles were synthesized in moderate yields (58–60%). For the reaction involving isocyanooacetate, the lactamination occurred spontaneously to provide ring-fused tetrazolo[1,5-a]pyrazin-6(5H)-one adducts 5 followed by intramolecular Heck reaction to give functionalized tetracyclic tetrazolo-pyrazino[2,1-a]isoquinolin-6(5H)-ones 6c–k in 73–79% yields. The electron-donating or electron-withdrawing groups on the aromatic ring didn’t show significant affect for the Heck reaction.

Products 6c–k were obtained in higher yields than products 6a–b. We believe that the secondary amine in intermediates 5 would affect the yield of Heck reaction. To address the issue, compounds 5 were N-alkylated to afford 7. Thus, an alternative one-pot synthesis for Ugi-azide/N-alkylation/Heck reactions was developed (Scheme 6). A mixture of 2-bromobenzaldehyde 1a (1 mmol), allylamine hydrochloride 2 (1 mmol), trimethylsilyl azide 3 (1 mmol) and benzyl isocyanide (1 mmol) in MeOH was reacted at 40 °C for 24 h. After evaporating the solvent, 3 mL CH₃CN was added to the crude 1,5-DS-1H-T 5a followed by the addition of 1 equiv of benzyl bromide and 2 equiv of K₂CO₃ for the
alkylation reaction at 80 °C for 3 h to give \(N\)-benzylated compounds \(7\). Finally, 10 mol% of \(\text{Pd(OAc)}_2\), 20 mol% of \(\text{PPh}_3\), 2 equiv of \(\text{K}_2\text{CO}_3\) were added to the reaction mixture for the Heck reaction at 105 °C for 3 h under \(\text{N}_2\) atmosphere to afford tetrazolyl-1,2,3,4-tetrahydroisoquinoline \(8\) in 74% isolated yield which is higher than the reaction of \(5\) for product \(6\) (58%). Under the alternative one-pot reaction conditions involving the step of \(N\)-alkylation, the substrate scope was explored by the preparation of 10 derivatives \(8\) using seven benzaldehydes (1), two isonitriles (4), and allylamine hydrochloride (2) with trimethylsilyl azide (3) for the Ugi-azide reaction. The \(N\)-alkylations were conducted using benzyl bromide and iodomethane, respectively. The final products \(8b-j\) were obtained in 66–74% yields.

To evaluate the scalability of the one-pot reaction protocol, we performed the synthesis of tetracyclic tetrazolo-pyrazino[2,1-\(a\)]isoquinolin-6(5\(H\))-one \(6c\) in gram quantity of \(1\) which led to the formation of product \(6c\) in a satisfactory yield of 77% (Scheme 7).

**Scheme 6:** One-pot synthesis for tetrazolyl-1,2,3,4-tetrahydroisoquinolines \(8\).

**Scheme 7:** Gram-scale one-pot synthesis of \(6c\).

Final products \(6\) and \(8\) were characterized by \(^1\text{H}\) and \(^{13}\text{C}\) NMR, HRMS analysis. In addition, single
crystals of compound 6d and 8c were obtained for X-ray analysis to confirm the structures (Figure 2).

![Figure 2: ORTEP diagrams of compound 6d (left) [CCDC: 2164364] and 8c (right) [CCDC: 2321622].](image)

**Conclusion**

In conclusion, we have developed a one-pot synthesis with two or three steps for making tetrazolo-pyrazino[2,1-a]isoquinolin-6(5H)-ones. The initial Ugi-azide four-component reaction is for making tetrazole while the intramolecular Heck reaction is for assemble tetrahydroisoquinoline. The one-pot reaction avoids the intermediate purification which has favorable PASE in the synthesis of heterocyclic compounds.

**Experimental**

**General procedure for the synthesis of Ugi-azide adducts 5a**

A solution of 2-bromobenzaldehyde 1 (1 mmol, 1 equiv), allylamine hydrochloride 2 (1 mmol, 1 equiv), trimethylsilyl azide 3 (1 mmol, 1 equiv) and tert-butyl isocyanide 4a (1 mmol, 1 equiv) in MeOH (5 mL) with Et₃N (1.5 mmol) was heated at 40 °C for 12 h in a sealed vial. Upon the reaction completed, the reaction mixture was filtered, then evaporating under vacuum to give crude products 5a. Further purification was conducted by flash chromatography with 1:6 petroleum ether/EtOAc to afford 5a in 92% yields. The adduct was confirmed and NMR.

**General procedure of Heck reaction for the synthesis of product 6a**

To a solution of Ugi-azide adduct 5a (0.1 mmol) with Pd(OAc)₂ (0.1 mmol), PPh₃ (0.2 mmol), K₂CO₃ (2 mmol) or NaOAc (2 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 with 1:4 ethyl acetate/petroleum ether to afford product 6a.
General procedure for the one-pot synthesis of tetrazole-containing 1,2,3,4-tetrahydroisoquinolines 6

A mixture of 2-bromobenzaldehyde 1 (1 mmol), allylamine hydrochloride 2 (1 mmol), trimethylsilyl azide 3 (1 mmol) and isocyanide 4 (1 mmol) was stirred in MeOH at 40 °C for 24 h, after the reaction was completed, the solvent was evaporated under vacuum to give crude Ugi adduct 5, without further purification, the crude intermediate 5 in MeCN (3 mL) was used for the Heck reaction with 10 mol% of Pd(OAc)$_2$, 20 mol% of PPh$_3$, 2 equiv of K$_2$CO$_3$ for 3 h at 105 °C under N$_2$ atmosphere. After aqueous work up, the crude product was purified by flash chromatography with 1:3 ethyl acetate/petroleum ether to afford product 6.

General procedure for the one-pot synthesis of tetrazolyl-1,2,3,4-tetrahydroisoquinolines 8

A mixture of 2-bromobenzaldehyde 1 (1 mmol), allylamine hydrochloride 2 (1 mmol), trimethylsilyl azide 3 (1 mmol) and isocyanide 4 (1 mmol) in MeOH was reacted at 40 °C for 24 h. After evaporating the solvent, 3 mL CH$_3$CN was added to the crude 1,5-DS-1H-T 5 followed by the addition of 1 equiv of benzyl bromide or iodomethane and 2 equiv of K$_2$CO$_3$ for the alkylation reaction at 80 °C for 3 h to give N-alkylated compounds 7. Finally, 10 mol% of Pd(OAc)$_2$, 20 mol% of PPh$_3$, 2 equiv of K$_2$CO$_3$ were added to the reaction mixture for the Heck reaction at 105 °C for 3 h under N$_2$ atmosphere, after aqueous work up, the crude product was purified by flash chromatography with 1:4 ethyl acetate/petroleum ether to afford product 8.

Supporting Information

Supporting Information File 1
General reaction procedures, compound characterization data, and copies of NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/xxxxxxxx.pdf]

Acknowledgements

We also thank Shaodong Jiang’s early work on this project.

References


54. Zhang, W.; Yi, W.-B. Pot, Atom, and Step Economy (PASE) Synthesis; Springer International Publishing: Cham, 2019


