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Authors	Jiawei Niu, Yuhui Wang, Shenghu Yan, Yue Zhang, Xiaoming Ma, Qiang Zhang and Wei Zhang
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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 Niu[1‡], Yuhui Wang[1‡], Shenghu Yan[1], Yue Zhang[1], 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

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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.

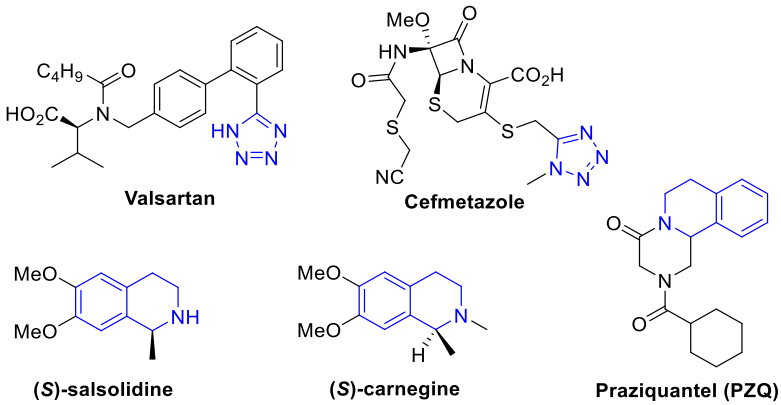
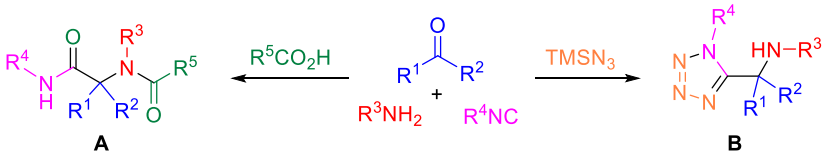
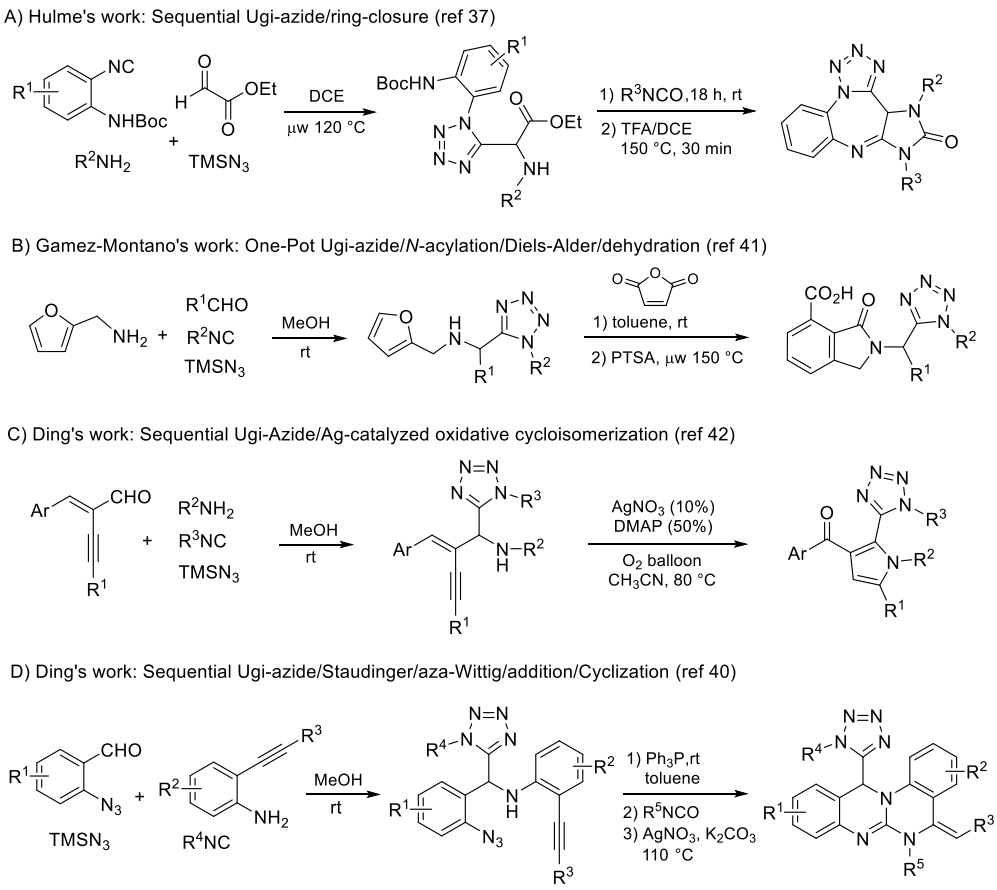


Figure 1: Representative bioactive tetrazole- and tetrahydroisoquinoline-containing compounds.

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 1*H*-tetrazoles (1,5-DS-1*H*-Ts) **B**. The performance of post-condensation reaction of UA-4CR adducts has resulted various 1,5-DS-1*H*-Ts containing heterocyclic compounds [28–32], such as bis-heterocyclic lactam-tetrazoles [33,34], 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-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*-quinazolino[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*)-5*H*-quinazolino[3,2-*a*]quinazolines (Scheme 2, D) [40].

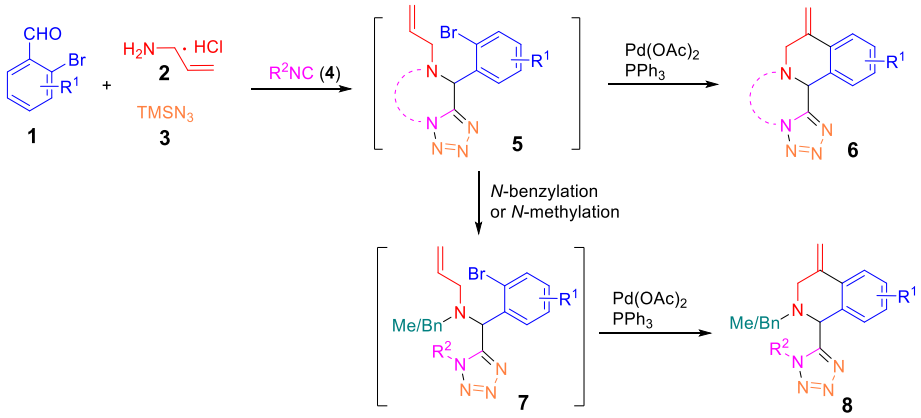


Scheme 1: The Ugi and Ugi-azide reactions.



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 ($TMSN_3$) **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(5*H*)-one adducts **5**. The Pd-catalyzed intramolecular Heck reaction of **5** or **7** afford 1,2,3,4-tetrohydroisoquinolines **6** and **8**, respectively.

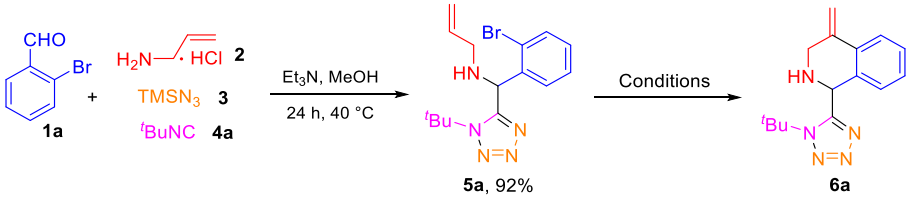


Scheme 3: One-pot synthesis of tetrazolyl-1,2,3,4-tetrahydroisoquinoline.

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-1*H*-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_3N in CH_3CN 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_2CO_3 was used as a base to replace Et_3N, the reactions in either CH_3CN 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_3PO_4, NaOAc and Cs_2CO_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_3CN 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_2CO_3 in 3 mL CH_3CN at 105 °C for 3 h under N_2 atmosphere which affords **6a** in 70% yield (entry 3).

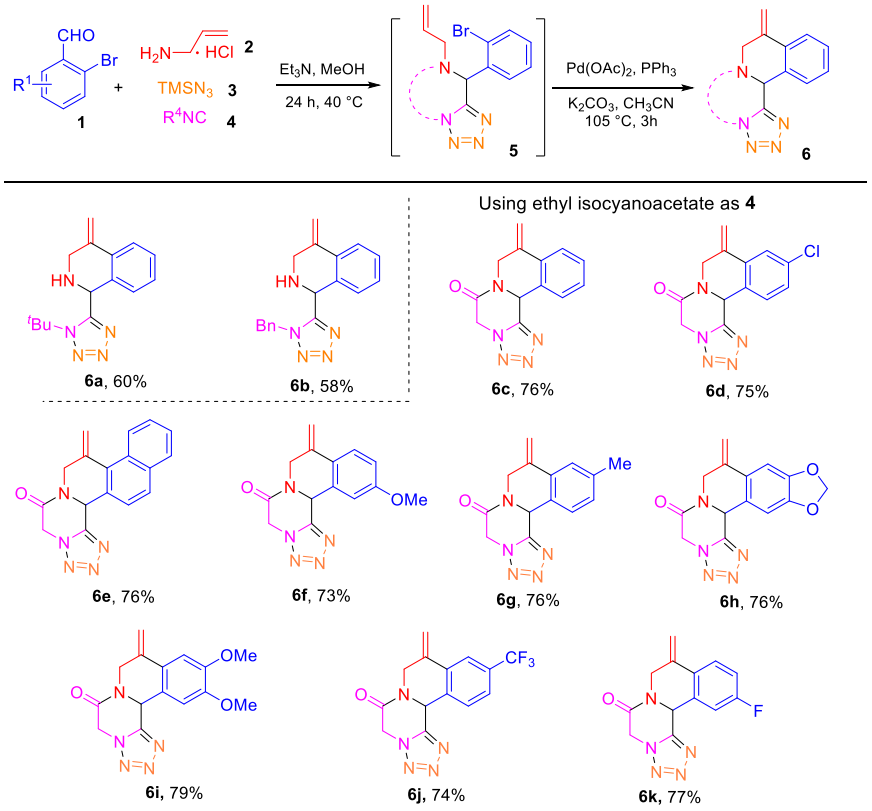
Table 1. Conditions for one-pot Ugi-azide and Heck reactions.[a]



Entry	Catalyst	Ligand	Solvent	Base	Temp (°C)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	MeCN	Et_3N	105	24	—
2	$Pd(OAc)_2$	PPh_3	DMF	Et_3N	105	24	—
3	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	105	3	70
4	$Pd(OAc)_2$	PPh_3	DMF	K_2CO_3	105	3	70
5	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	105	12	65
6	$Pd(OAc)_2$	—	MeCN	K_2CO_3	105	6	35
7	$Pd(OAc)_2$	PCy_3	MeCN	K_2CO_3	105	6	46
8	$Pd(OAc)_2$	$P(o\text{-tol})_3$	MeCN	K_2CO_3	105	6	56
9[c]	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	105	3	58
10	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	70	8	60
11	$Pd(OAc)_2$	PPh_3	MeCN	K_2CO_3	120	3	62
12	$Pd(OAc)_2$	PPh_3	MeCN	K_3PO_4	105	3	39
13	$Pd(OAc)_2$	PPh_3	MeCN	NaOAc	105	3	62
14	$Pd(OAc)_2$	PPh_3	MeCN	Cs_2CO_3	105	3	56
15	$PdCl_2$	PPh_3	MeCN	K_2CO_3	105	5	53
16	$Pd(dba)_2$	PPh_3	MeCN	K_2CO_3	105	6	61
17[d]	**$Pd(OAc)_2$**	**PPh_3**	**MeCN**	**K_2CO_3**	**105**	**3**	**60**

[a] Reaction conditions: Ugi-azide step, 2-bromobenzaldehyde **1a** (1 mmol), allylamine hydrochloride **2** (1 mmol), trimethylsilyl azide **3** (1 mmol) and *tert*-butyl isocyanide **4a** (1 mmol), Et_3N (1.2 mmol) in 5 mL MeOH, 40 °C for 24 h. Heck step, catalyst (10 mol%), ligand (20 mol%), solvent (3 mL), base (2 equiv), nitrogen atmosphere. [b] Isolated yield. [c] $Pd(OAc)_2$ 5 mol%, PPh_3 10 mol%. [d] Reaction was carried out in one-pot, starting compound is **1a** (1 mmol), first Ugi-azide reaction followed by the Heck reaction.

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 PPh_3, 2 equiv of K_2CO_3 for 3 h at 105 °C under N_2 atmosphere to give **6a** in 60% isolated yield (entry 17).

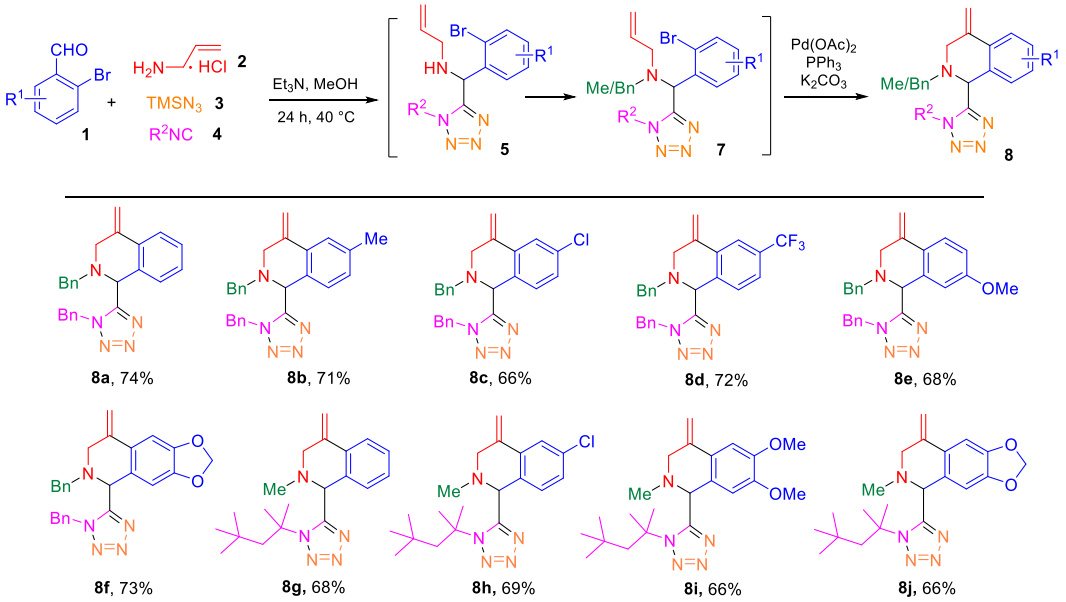


Scheme 5: One-pot synthesis for the tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-ones **6**.

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 isocyanoacetate **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 isocyanoacetate, the lactamination occurred spontaneously to provide ring-fused tetrazolo[1,5-*a*]pyrazin-6(5*H*)-one adducts **5** followed by intramolecular Heck reaction to give functionalized tetracyclic tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-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.

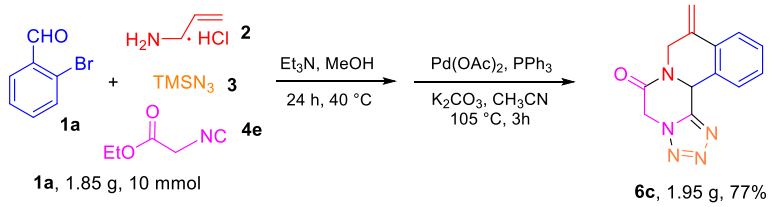
Products **6c**–**k** were obtained in higher yields than products **6a**–**b**. We believe that the secondary amine in intermediates **5** would affect the yield of Heck reaction. To address the issue, compounds **5** were *N*-alkylated to afford **7**. Thus, an alternative one-pot synthesis for Ugi-azide/*N*-alkylation/Heck 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 CH_3CN was added to the crude 1,5-DS-1*H*-T **5a** followed by the addition of 1 equiv of benzyl bromide and 2 equiv of K_2CO_3 for the

alkylation reaction at 80 °C for 3 h to give *N*-benzylated compounds **7a**. Finally, 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3, 2 equiv of K_2CO_3 were added to the reaction mixture for the Heck reaction at 105 °C for 3 h under N_2 atmosphere to afford tetrazolyl-1,2,3,4-tetrahydroisoquinoline **8a** in 74% isolated yield which is higher than the reaction of **5d** for product **6b** (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 **8a**–**j** (Scheme 6) 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.



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

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 **1a** which led to the formation of product **6c** in a satisfactory yield of 77% (Scheme 7).



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

Final products **6** and **8** were characterized by ^1H and ^{13}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).

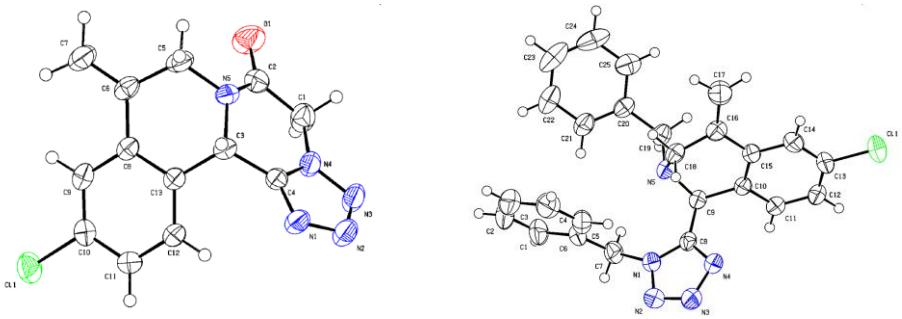


Figure 2: ORTEP diagrams of compound **6d** (left) [CCDC: 2164364] and **8c** (right) [CCDC: 2321622].

Conclusion

In conclusion, we have developed a one-pot synthesis with two or three steps for making tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-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 Et_3N (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), PPh_3 (0.2 mmol), K_2CO_3 (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_2CO_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_3CN was added to the crude 1,5-DS-1*H*-T **5** followed by the addition of 1 equiv of benzyl bromide or iodomethane and 2 equiv of K_2CO_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_2CO_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]

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